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OBSERVATIONS ON THE CLINICAL FEATURES AND NEUROLOGICAL MECHANISM OF SPONTANEOUS NYSTAGMUS RESULTING FROM UNILATERAL ACOUSTIC NEUROFIBROMATA

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1 The results are described of a study of the spontaneous horizontal nystagmus found to be present in 75 subjects with unilateral acoustic neurofibromata

2 For convenience of analysis all tumors of the *right* nerve were considered as tumors of the *left* with transposition of the laterality of the nystagmus and other physical signs In effect therefore the material consisted of 75 subjects with left sided tumors

3 The nystagmus was classified according to convention in terms of its direction and degree

4 In many of the subjects nystagmus was present both to left and to right In these and others there was a clear preponderance of the nystagmus to the right

5 Electronystagmographic analysis of the spontaneous nystagmus was carried out in a representative selection of subjects In contrast with that found to follow unilateral destruction of the VIII nerve or labyrinth the nystagmus was found to be inhibited by the elimination of visual fixation whether by darkness or eye closure with return of the eyes from their deviated position to a rest position nearer to the straight ahead line If however in the absence of visual fixation eye deviation in the direction of the subject s own thumb was maintained by means of the proprioceptive mechanisms the nystagmus was found to persist although with some reduction of its frequency and regularity

6 In view of the finding that the nystagmus was dependent not upon fixation *per se* or other visual mechanisms but rather upon the maintenance of conjugate eye deviation the proposal is made that it should be defined as deviation maintenance nystagmus

7 The nystagmus is considered to be due to damage resulting from tumor pressure of certain brain stem mechanisms which have to do with the control of conjugate eye deviations in the horizontal plane

One such mechanism is that of the vestibular tonus elements thought to lie caudally within the vestibular nuclear complex Tumor pressure tends to affect these early and is the cause of the deviation maintenance type of nystagmus to the right

The second mechanism is that concerned with voluntary conjugate eye deviation to the left As described by Bender & Shanzer (1964) the neural elements which subserve this mechanism occupy a position on

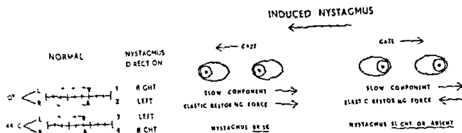


Fig 1

Fig 2 The mechanism of Alexander's law

2 *The neurological mechanism of directional preponderance its relationship to vestibular tonus imbalance and to the operation of Alexander's law*

The mechanism of D P , occurring as the result of damage to certain vestibular elements within the brain stem has been the subject of a recent study by Carmichael, Dix & Hallpike (1965) Their material consisted of a series of patients with vascular occlusive lesions of the lateral zone of the medulla All exhibited the clinical features of Wallenberg's syndrome, and in all a D P of the caloric responses was present to the opposite side

Reconstruction of the neuro anatomy of the lesions led to the conclusion that this preponderance was due to the involvement of certain elements of the vestibular nuclei, lying caudally within the nuclear complex which were thought to be associated with the tonus mechanism of the ipsilateral labyrinth—in all probability of the utricle

The explanation proposed of the way in which such a lesion was able to bring about the directional preponderance of caloric nystagmus, was based upon the view that the utricular tonus elements, left and right, exert a pair of forces, opposed and balanced, upon the conjugate deviation of the eyes, the left elements subserving deviation to the right, the right elements to the left

From this it would follow that damage to the left elements would bring about a latent deviation of the eyes to the left, and for the occurrence of this some evidence was adduced Thus, nystagmography carried out in the absence of visual or other forms of conscious fixation, showed in some patients a clear tendency to deviation to the side of the lesion

The way in which such a vestibular tonus imbalance and its consequent latent deviation of the eyes might bring about a D P of caloric nystagmus was explained by Carmichael, Dix & Hallpike (1965) in terms of what is known as Alexander's law According to this, nystagmus of the vestibular type whether spontaneous or induced, is increased by voluntary deviation of the [illegible] agmus Deviation in [illegible] is commonly explain[illegible] involving the elastic and other forces, some neuromuscular in nature, others purely mechanical and originating in the orbital

the left side of the brain stem above the level of the vestibular nuclei Tumor pressure tends to affect them a little later than the vestibular tonus elements, and is the cause of the deviation maintenance type of nystagmus to the left

Damage to other brain stem mechanisms is thought to play a significant but subsidiary role in the genesis of the spontaneous nystagmus These include the reticular components known to be associated with the vestibular elements, and also the numerous cerebellar efferents to the vestibulo ocular and oculomotor systems

INTRODUCTION

Spontaneous nystagmus, one of the best known manifestations of an Acoustic Neurofibroma, is generally held to result from tumor pressure upon the brain stem, and it is the purpose of the present study to attempt an analysis of its neurological mechanism

The subject is a complex one and the following closely related matters will first be considered

1 The phenomenon of directional preponderance of induced nystagmus
2 The neurological mechanism of directional preponderance, its relationship to vestibular tonus imbalance and to the operation of Alexander's law
3 The pathophysiology of the Spontaneous Nystagmus which follows unilateral section of the VIII nerve

1 *The phenomenon of directional preponderance of induced nystagmus*

In Fig 1 is shown the average normal pattern of the caloric responses induced and recorded according to the standardised procedure of Fitzgerald & Hallpike (1942) The continuous lines represent time–3 minutes subdivided into 10 second intervals The interrupted lines are the response durations Above are the responses left and right, to the cold stimulus, below, the responses to the hot stimulus If, for convenience, these responses are numbered 1–4 from above downwards, then 1 and 4 consist of nystagmus to the right, 2 and 3 of nystagmus to the left

Two primary abnormalities, canal paresis and directional preponderance, result from a unilateral lesion of the vestibular system at or below the level of the vestibular nuclei Whether such a lesion affects the sense organs, the nerve fibres or the nuclei, either *one* of these abnormalities may be the result and it has therefore been argued that they must depend upon damage to elements which at all levels are anatomically discrete (Hallpike, 1957)

By Directional Preponderance (D P) the abnormality to be considered, is meant the facilitation of those responses which consist of nystagmus in a particular direction with inhibition of their opposites

Thus, with D P to the right, responses 1 and 4 are increased responses 2 and 3 reduced With D P to the left, this pattern is reversed



Fig 4 Rabbit showing typical disturbance of posture following destruction of the left labyrinth (Magnus)

3 *The pathophysiology of the spontaneous nystagmus and other disturbances which follow unilateral destruction of the VIII nerve*

In Fig 4 taken from Magnus monograph (1924) is shown a rabbit shortly after destruction of the left labyrinth The ipsilateral limbs are flexed the contralateral limbs extended The neck is turned to bring the *affected labyrinth* undermost and spontaneous nystagmus is present to the *right* The condition is rapidly modified by the operation *of certain processes of* central compensation The nystagmus ceases and the neck *torsion* diminishes The *course* pursued by the abnormalities of neck and limb posture varies in different species Thus while in the rabbit *the neck torsion is usually* severe and its correction incomplete in man it is seldom a conspicuous *feature In all* species however the disappearance of the spontaneous nystagmus is regularly *observed*

It is possible *to suggest that* in this course of events two mechanisms are concerned Of *these one is* dependent upon the horizontal canals and is directly concerned in inducing *nystagmus* It is intrinsically nystagmogenic The second has to do with sustained conjugate eye deviations and is dependent upon the otolith organs Though not directly concerned in inducing nystagmus *it may* exert a directional effect upon it when induced through the canal *mechanism* The canal mechanism will first be considered

As revealed by the work of Lowenstein & Sand (1940) the sense organs of each of the horizontal canals *are the source of* a resting nervous discharge while from other *evidence* it is known that this tends to produce nystagmus to its own *side the* slow component being directed towards the opposite side Normally the *action of each canal* is opposed and balanced by that of its opposite and nystagmus only occurs if the balance is upset

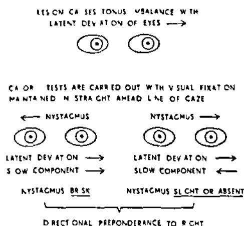


Fig 3 The mechanism of the directional preponderance to the right of caloric nystagmus resulting from a lesion of the left vestibular tonus elements

tissues, which combine to resist deviation of the eyes from their resting *mid-line position and to restore them thereto*

Thus, in a subject who in the straight ahead position of the eyes exhibits vestibular nystagmus to the right, there will be rapid beats to the right alternating with slow components of vestibular origin to the left With voluntary deviation of the eyes to the right, the elastic restoring forces of the orbital tissues will supplement the slow components Hence, their amplitude and that of the nystagmus as a whole will be increased With deviation of the eyes to the left, however, the elastic restoring force will be directed to the right and will oppose the slow components of the nystagmus Its amplitude will accordingly be reduced A diagrammatic representation of the situation is presented in Fig 2

These principles were applied by Carmichael, Dix & Hallpike (1965) to the explanation of the directional preponderance of caloric nystagmus to one side, e g, the right, resulting from a lesion of the left tonus elements within the brain stem Accepting the view that the primary effect of this lesion was a deviation to the left of the resting position of the eyes these authors argued that the voluntary assumption by the subjects of the straight ahead position of the eyes used for the caloric tests could be equated to their deviation in the direction of the nystagmus to the right Latent deviation of the eyes to the left would still be present and would then operate in accordance with Alexander's law facilitating nystagmus to the right and hence the directional preponderance To put the matter in detail with caloric nystagmus to the right, the latent deviation of the eyes to the left would supplement the slow component of the nystagmus and so increase it With caloric nystagmus to the left however, the slow component of the nystagmus being directed to the right, would be opposed by the latent deviation and so the nystagmus would be reduced

The matter is explained diagrammatically in Fig 3

of these canals If the discharge of one canal, e g, the left is interrupted by division of the left VIII nerve, a canal imbalance nystagmus will result As to the process which brings about its disappearance, here it is said that the left nuclear elements, being deprived of the resting discharge from the left canal, are in some way able to establish an activity of their own In this way their output is brought into balance with that of the right nuclear elements and the nystagmus ceases If, now, a lesion is made of the left nuclear elements themselves the state of imbalance is restored, and with it the nystagmus returns and is now more lasting

Accepting this as the part played by the horizontal canals and their associated nuclei in the nystagmic sequelae of unilateral VIII nerve destruction, it is nevertheless evident that another factor to be considered is that which must arise from the loss of the vestibular tonus effects considered by Carmichael, Dix & Hallpike (1965) to exert a certain controlling effect upon conjugate eye deviations As will later be argued, this factor is one of considerable importance

It will be understood that, in addition to destroying the peripheral neurones of the VIII nerve, an acoustic neurofibroma will, at a later stage, exert pressure upon and damage its central connections within the brain stem These will include both the nuclear elements associated with the horizontal canals and their nystagmic activities, and also the more caudally placed vestibular tonus elements which, as already explained, have to do with the sustaining of conjugate deviations of the eyes To this must be added another factor of considerable importance—the organic derangement of those elements of the reticular system the activity of which, as shown by the electrophysiological studies of Duensing (1962) is so closely associated with that of the vestibular neurones Since it is at this stage of the tumor's development that the spontaneous nystagmus of a patient with an acoustic neurofibroma so typically makes its appearance, it follows that for the analysis of its neurological mechanism the relevance of the foregoing anatomical and physiological considerations requires no emphasis

A note on the pathology and early development of the acoustic neurofibroma

As shown by Hardy & Crowe (1936) this seems to originate in the vestibular elements of the VIII nerve in the region of Scarpa's ganglion and for a time, often a long time, is confined to the region of the porus acusticus In this, the first or otological stage of its development, the clinical course of the tumor is notoriously insidious For this the reason is that the destruction of the vestibular nerve is very slow, and with it the process of central compensation is able to keep pace Hence, a patient may well progress to the point of complete destruction of the vestibular nerve without at any time experiencing any symptoms of vestibular dysfunction

The tumor then enters upon its second or neurological stage It emerges from the porus acusticus, presses upon the brain stem and this is the

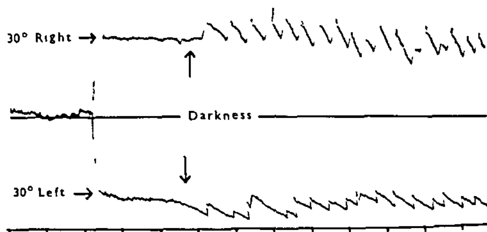


Fig. 5. Electronystagmographic recordings of Caloric Nystagmus to the right, showing (A) Brisk enhancement of nystagmus with abolition of visual fixation. (B) Enhancement and inhibition of nystagmus with conjugate deviations to the right and left (Alexander's law).

Now, this can be done in several ways. Thus, hot caloric stimulation of the right canal increases its resting discharge and causes nystagmus to the right. To stop it the balance must be restored. This can be done by stopping the stimulus or, as well, by applying an equal hot stimulus to the left canal. The same imbalance will result from destruction of one horizontal canal or its nerve, either in isolation or as part of a labyrinth destruction or VIII nerve section. Again, the result will be nystagmus to the opposite side.

It need hardly be said that one of the early effects of an VIII nerve tumor is to destroy the VIII nerve, and in due course consideration will be given to the possibility that the nystagmus of an VIII nerve Tumor could be explained in terms of canal imbalance.

Canal imbalance nystagmus has certain well known nystagmographic features, being checked by visual fixation and enhanced without it.

In Fig. 5 are shown some records of canal imbalance nystagmus resulting from hot caloric stimulation of the right horizontal canal. The records were taken just at the end of the reaction, and no nystagmus is therefore visible while fixation is maintained either with the eyes straight ahead or to the right or left. At the points indicated, visual fixation is eliminated by darkness and brisk nystagmus to the right appears. In accordance with Alexander's law it is more marked with the eyes deviated to the right than to the left.

Attention may now be given to the processes of central compensation, to which it is customary to attribute the spontaneous disappearance of this canal imbalance nystagmus which follows a unilateral section of the VIII nerve.

At rest the elements of the vestibular nuclei which are associated with the horizontal canals receive the resting discharges, equal and opposite,

TABLE 1 *Directional characteristics of the spontaneous horizontal nystagmus in 75 cases of neurofibroma of the left VIII nerve*

Groups	1	2	3	4	5	6	7
Nystagmus	1st degree only to left	2nd degree only to left	2nd degree to left 1st degree to right	1st degree to left 1st degree to right	1st degree to left 2nd degree to right	2nd degree only to right	1st degree only to right
Number of cases	4[a]	0[a]	1[a]	35	14[b]	5[b]	16[b]

[a] Nystagmus wholly or preponderantly to left 5 cases
[b] Nystagmus wholly or preponderantly to right 35 cases

Certain characteristics of the nystagmus, as observed in the course of routine clinical examination are worthy of note Thus, whether this was found to be equal to both sides or preponderant to the right, it was nearly always possible to observe that the nystagmus to the left was rather slower and a little less regular than that to the right However, this difference might be small and it must be said, too, that both to left and right the nystagmographic wave forms usually presented a striking similarity

The central problem, the neurological mechanism of the nystagmus may now be considered Here, an obvious point of enquiry is the extent to which a canal imbalance could play a part If so, this could hardly arise from destruction of the VIII nerve itself, since with the slow rate of its destruction no imbalance at the nuclear level could develop, an inference which is validated by the very common finding of complete loss of the left caloric responses in the absence of any spontaneous nystagmus

As a further possibility, a canal imbalance might be expected to result from tumor pressure affecting the canal elements of the left vestibular nuclei For this there is some nystagmographic evidence Thus, in some cases of Group 7, in whom the nystagmus was of the 1st degree only to the right, this was sometimes found to display to a minor degree the same enhancement in darkness as that which follows section of the left VIII nerve However, the finding was not a common one, and was considered to be a transient stage in the development of the nystagmus into its characteristic bilateral form

It was accordingly concluded that although canal imbalance may play a part in the early stages of the spontaneous nystagmus of an VIII nerve tumor, the part is a small one Other and more important mechanisms are concerned and on the nature of these, nystagmographic studies have provided much information

stage reached by all of the patients with spontaneous nystagmus who have provided the material for the present study.

MATERIAL, METHODS OF STUDY AND RESULTS

The selection of cases, 75 in all, has been limited to those, by far the most common, in which the nystagmus occurred only in the horizontal plane. Furthermore, in order to simplify analysis and discussion it has been found expedient to consider all tumors of the right VIII nerve as if they were tumors of the left, and to transpose accordingly the laterality of their nystagmus and other relevant signs.

The material for analysis may therefore be said to consist of 75 cases *of neurofibroma of the left VIII nerve.*

As shown in Table 1, the 75 cases have been divided into 7 groups depending upon the direction of the nystagmus. This was observed under good illumination with the subject's head erect, deviation of gaze being induced *by following of the observer's finger to left and right within limits which* did not exceed 30 degrees from the straight ahead line.

The terms "1st degree" and "2nd degree" have been applied to the nystagmus in accordance with convention. Thus nystagmus to the left is said to be of the 1st degree when present only with gaze to the left; of the 2nd degree when present both with gaze to the left and, to a lesser extent, in the straight ahead line.

In the largest of the 7 groups shown in Table 1, the nystagmus was symmetrical, being of the 1st degree to left and right. Groups 5, 6 and 7 were all large and comprised 35 cases in which the nystagmus was preponderantly to the right.

Groups 1, 2 and 3, however, were very small, comprising only 5 cases *in which the nystagmus was preponderantly to the left.*

These data establish the fact that the nystagmus is essentially bilateral, occurring, that is to say, with gaze deviation either to left or to right. Furthermore, there is a marked preponderance of the nystagmus to the right. It is believed, too, that in the majority of cases the character of the nystagmus tends to develop in a certain sequence; that it appears first as Type 7, developing, it may be, into Type 4, but often into Type 5. This cannot, of course, be stated with certainty, since in many cases the nystagmus type recorded was that seen at the first and only examination. In consequence, if a case of Group 5 be taken as an example, it could be claimed that the nystagmus from the time of its first appearance had been present unchanged in this particular form.

While this possibility cannot be denied, the strong directional pattern of the data in this table, together with the fact that the sequence in question has been actually observed in some of the subjects, strengthens the belief that it is generally followed in the others.

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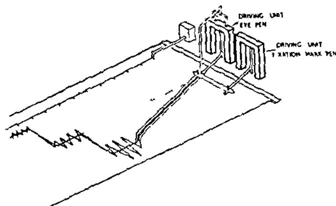


FIG 7 Pen assembly for coincident recording of deviations of eyes and fixation point

With this equipment rapid and accurate observations can be made of the effect upon spontaneous nystagmus of eye deviations carried out with *visual fixation* maintained Furthermore, it is possible to observe the various and important effects of abolishing visual fixation by means of darkness or eye closure Thus, spontaneous nystagmus may be altered in *magnitude* if it is present, or induced if it is not In addition, clear recordings are obtained of any sustained conjugate deviations which may *occur*

In Fig 7 is shown the arrangement of the recording pens which has been found very convenient Their rotational axes are actually and their writing points virtually coincident The outer pen records the angular deviation of the fixation mark Upwards and downwards deflections of this pen from the central base line correspond respectively to deviations to right and left of the fixation mark

The inner or eye pen records the conjugate eye movements in the horizontal plane The sensitivity of its amplifier is adjusted to match that of the fixation mark pen, and both work to the same central base line The system has the great practical advantage of making it very easy to observe at any point upon the record, the accuracy with which the eyes are maintaining any prescribed deviation

The recording shown in Fig 7 is from a subject with 3rd degree vestibular nystagmus to the left Thus, with visual fixation on the mark deviated 20 degrees to the right, slight nystagmus is present with its rapid component to the left It increases greatly in amplitude when the eyes follow the fixation mark to a point 20 degrees to the left

2 Nystagmographic findings

In Fig 8 are shown the recordings obtained in a characteristic case This was taken from Group V of the series, and therefore exhibits 2nd degree nystagmus to the right with 1st degree nystagmus to the left



Fig. 6. Equipment and test procedure for electro-nystagmographic investigation of spontaneous nystagmus.

Nystagmographic Investigation of the Spontaneous Nystagmus

1. *Technique*

As previously described (Hallpike, Hood & Trinder, 1960) direct current amplification, using the so-called chopper technique, has been preferred for the electro-nystagmographic recording of the nystagmus. In Fig. 6 is shown the test procedure. The subject, wearing the electrode assembly, sits with his head firmly immobilised. In front of him, carried upon a vertical rod, is a visual fixation mark. The rod is connected to a handle, held in the examiner's left hand, and with it he can deviate the fixation mark by known amounts—10, 20 or 30 degrees—to the subject's left or right. The points are selected by touch. This is achieved by means of a spring-loaded ball which is carried upon the handle and engages a series of recesses suitably spaced upon the circumference of a steel half-circle.

In this way, the examiner, sitting behind the subject, is enabled without removing his gaze from the recording pens, to set the fixation mark upon any of the fixed points desired.

At the bottom of the vertical post is a rest. With his hand upon this the subject's thumb can be supported in the position of the fixation mark and can be carried round to his left or right. In certain circumstances, the subject, after fixing his gaze upon the fixation mark, deviated either to right or left, may be asked to maintain this deviation in darkness or with eye closure.

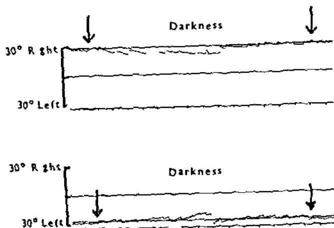


Fig 10 Electro-nystagmographic recordings Subject C W D showing effects upon the spontaneous nystagmus of abolishing visual fixation alone The subject in darkness maintains voluntary deviation of his eyes upon his own thumb by *means of his proprioceptive* mechanisms The nystagmus persists but becomes slow and irregular (compare Fig 8)

gaze upon his thumb deviated to right and left, with resultant nystagmus *in both* directions Between the arrows there is darkness and the patient makes no attempt to maintain deviation of his eyes upon his thumb by means of his proprioceptive mechanisms Both from the left and the right the eyes swing back towards a rest position nearer to the mid line and the nystagmus ceases

The records shown in Fig 10 demonstrate the effect upon the nystagmus of a rather different test procedure First the subject *in the light,* fixes his gaze upon his thumb deviated to right and left Initially there is 1st degree nystagmus in both directions Between the arrows visual fixation is *abolished but* the subject then endeavours to maintain deviation upon his thumb by means of his proprioceptors It will be seen that both to the right and to the left the conjugate ocular deviations are quite well maintained and with this some nystagmus *persists* Its character, however changes It now has a larger amplitude but it is irregular and a great deal slower particularly in respect of the speed of its slow component

DISCUSSION

It is clear that this kind of nystagmus differs radically from the canal imbalance nystagmus *which follows* section of the VIII nerve In that, it will be *recalled* the nystagmus tends to be suppressed by visual fixation but is enhanced *without* it

The nystagmus recordings presented in the preceding three figures represent a very *different* situation The elimination of fixation far *from*

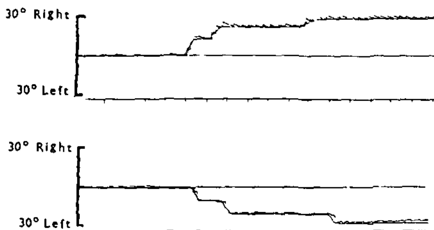


Fig 8 Electro nystagmographic recordings of spontaneous nystagmus (2nd degree to right 1st degree to left) in a subject (C W D) with a left acoustic neurofibroma showing the effects upon the nystagmus of conjugate eye deviations with maintenance of visual fixation

The records were taken in the light with the eyes open, with visual fixation maintained upon the subject's thumb, supported before him as described upon a rest at various known angular deviations to left and right of the straight ahead line

With gaze straight ahead slight but definite nystagmus is shown to the right With gaze to the right nystagmus is increased, well sustained and extremely regular With gaze to the left 1st degree nystagmus to the left is present It has a rather smaller amplitude than that to the right Its frequency, too, is less and also the speed of its slow component

The records shown in Fig 9 show the effect upon the nystagmus of *abolishing fixation First, as before, the subject in the light fixes his*

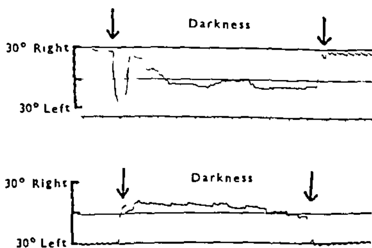


Fig 9 Electro nystagmographic recordings Subject C W D showing effects of darkness upon the spontaneous nystagmus Voluntary deviation of the eyes either by means of visual fixation or the proprioceptive mechanisms is not maintained and the nystagmus ceases

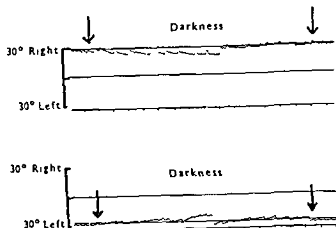


Fig 10 Electro nystagmographic recordings Subject C W D showing effects upon the spontaneous nystagmus of abolishing visual fixation alone The subject, in darkness, maintains voluntary deviation of his eyes upon his own thumb by means of his proprioceptive mechanisms The nystagmus persists but becomes slow and irregular (compare Fig 8)

gaze upon his thumb deviated to right and left, with resultant nystagmus in both directions Between the arrows there is darkness, and the patient makes no attempt to maintain deviation of his eyes upon his thumb by means of his proprioceptive mechanisms Both from the left and the right the eyes swing back towards a rest position nearer to the mid line and the nystagmus ceases

The records shown in Fig 10 demonstrate the effect upon the nystagmus of a rather different test procedure First, the subject, in the light, fixes his gaze upon his thumb deviated to right and left Initially there is 1st degree nystagmus in both directions Between the arrows visual fixation is abolished, but the subject then endeavours to maintain deviation upon his thumb by means of his proprioceptors It will be seen that both to the right and to the left the conjugate ocular deviations are quite well maintained and with this some nystagmus persists Its character, however changes It now has a larger amplitude, but it is irregular and a great deal slower, particularly in respect of the speed of its slow component

DISCUSSION

It is clear that this kind of nystagmus differs radically from the canal imbalance nystagmus which follows section of the VIII nerve In that, it will be recalled, the nystagmus tends to be suppressed by visual fixation but is enhanced without it

The nystagmus recordings presented in the preceding three figures represent a very different situation The elimination of fixation, far from

enhancing the nystagmus, tends to abolish it. Expressed in reverse, the nystagmus is increased by fixation and seems to depend upon it.

In this respect it is indistinguishable from that described by Holmes (1917) in subjects with unilateral cerebellar lesions. To it he applied the term "fixation" nystagmus. Kestenbaum (1948) on the other hand, in his discussion of the spontaneous nystagmus—in all probability of identical type—in subjects with organic affections of the brain stem, seems to prefer the term gaze nystagmus.

This use of these terms, gaze and fixation, cannot be accepted without demur, since both so clearly import and should be reserved for the action of purely visual mechanisms. But, as will be seen from the nystagmographic records, the nystagmus is determined not by fixation *per se* but rather by the maintenance of a certain conjugate deviation. If, for its maintenance, the visual fixation mechanism is used, then the deviation is well maintained, with nystagmus which is rapid and of small amplitude. If, in the absence of vision, the deviation is maintained by means of the proprioceptive mechanism, then, certainly, the nystagmus still occurs. Nevertheless, the deviation control is now less precise and the nystagmus is therefore less regular and of larger amplitude. Since, therefore, the nystagmus depends upon the maintenance of conjugate deviation, it seems both correct and convenient to designate it a deviation maintenance nystagmus.

The neurological mechanism of the spontaneous nystagmus

Accepting this specification of its characteristics, it remains to consider its neurological mechanism. Two of its features require explanation: firstly, why the tumor, by virtue of its growing pressure upon the left side of the lower brain stem, should produce in definite succession, first, nystagmus to the right followed closely by nystagmus to the left. Secondly, why the nystagmus both to right and left should be of the deviation maintenance type.

As will be contended, the answers to these questions are to be found in the derangement, resulting from tumor pressure of certain brain stem mechanisms which regulate conjugate eye deviation in the horizontal plane, a phrase which, for simplicity, will be abbreviated to the single word "deviation".

The subject is one of great complexity, and has been notably illuminated by the work of Bender & Shanzer (1964). They used the electrical stimulation technique in monkeys and among the matters which they considered was the contralateral deviation which, as known from the time of Ferrier, is brought about by stimulation of one cerebral hemisphere. Although Bender confirmed the occurrence of the deviation, he found little to validate the opinion that it is dependent upon certain localised regions of the hemisphere such as Area 12 of the frontal cortex which has for so long figured in text book treatments of the subject. Instead, he inclined to the view that the



Fig. 11. Brain stem diagrams (Hyde) showing position occupied by neurones subserving ipsilateral voluntary conjugate eye deviations.

deviation depends upon a mechanism which is much more diffusely distributed throughout the hemisphere.

Bender also provided valuable information upon the topography of the pathways from hemisphere to brain stem whereby this deviation mechanism is subserved. He concluded that above the level of the oculomotor nuclei the pathway is ipsilateral in respect of the activating hemisphere. Just below this level, however, it crosses to the opposite side and continues caudally to below the level of the VI nerve nuclei. In other words, the pathway for left deviation crosses the mid line just below the level of the oculomotor nuclei. Above this level it lies on the right, below it on the left.

The conclusions of Jane Hyde (1964) accord very closely with those of Bender. Hyde also used the electrical stimulation technique and was able to identify a left deviation mechanism on the right side of the brain stem near to the superior corpus quadrigeminum. This could be traced downwards across the mid line to the left side of the lower brain stem.

The topography of the pathways is shown in the brain stem diagrams which are reproduced in Fig. 11 from Hyde's paper. Her observations certainly seem to show that voluntary deviation to the left is subserved by this ipsilateral pathway within the pons and medulla. In this situation it is clearly vulnerable to pressure by a left acoustic neurofibroma in the neurological stage of its development with consequent weakness of sustained voluntary ipsilateral deviation.

This voluntary deviation mechanism is not, of course, the only one that needs to be considered. Other brain stem mechanisms are likely to be concerned and include the vestibular tonus system studied by Carmichael, Dix & Hallpike (1965). Its cell elements appear to be situated caudally in the vestibular nuclear complexes and are likely there to be vulnerable to pressure from a tumor of the VIII nerve. As already explained, any unresolved lesion of these elements will bring about a state of tonus imbalance with ipsilateral deviation of the eyes, e.g., in the case of a left sided acoustic neurofibroma the effect to be expected would be a deviation to the left.

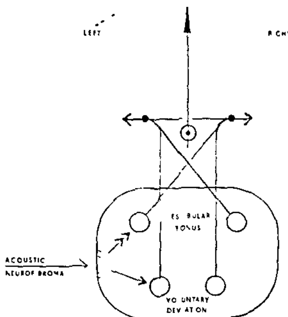


Fig 12 Diagram showing the sequential effects of a left acoustic neurofibroma upon the brain stem mechanisms which are concerned with the control of conjugate eye deviations in the horizontal plane These are (1) The vestibular tonus elements (2) The voluntary deviation elements

In Fig 12 is shown a diagrammatic reconstruction of the effects of a left acoustic neurofibroma in unbalancing the voluntary and vestibular tonus mechanisms within the brain stem which are concerned with the control of eye deviation in the horizontal plane It includes both the voluntary deviation elements at a level rather above the VI nerve nuclei, together with the vestibular tonus elements at a lower level

The eyes are represented by the pointer On it, each voluntary mechanism exerts an ipsilateral, each vestibular mechanism a contralateral, pull With deviation to the right the right voluntary mechanism acts with the left vestibular mechanism, their opposites being inhibited

Clearly, if both voluntary mechanisms are weakened there will be weakness of deviation in either direction But the same or similar result would accrue if both vestibular mechanisms are weakened, since in this event with deviation in either direction the operative voluntary mechanism would be deprived of the normal supporting action of its associated vestibular mechanism

The effect upon these elements of a left acoustic neurofibroma in its neurological stage would in most cases be exerted upon the vestibular mechanism with resultant weakening of contralateral deviation This would explain the Deviation Maintenance type of nystagmus to the right which is usually the first to appear At this time or a little later, the left voluntary mechanism would also begin to be affected This would cause weakness of ipsilateral deviation and would explain the deviation maintenance type

of nystagmus to the left which is so characteristic of the later stages of the tumor

The explanation thus provided of the characteristics and neurological mechanism of the spontaneous nystagmus of a left acoustic neurofibroma in the neurological stage of its development can now be summarised as follows: Tumor pressure first affects the left vestibular tonus elements and causes a Deviation Maintenance type of spontaneous nystagmus to the right At the same time, but usually a little later, the left voluntary deviation elements are affected, and this causes the Deviation Maintenance type of spontaneous nystagmus to the left Both to right and to left the nystagmus is due to weakening of a deviation mechanism Hence, in both directions the nystagmus is of the Deviation Maintenance type Certain differences can usually be observed Thus, the ipsilateral nystagmus may be noticeably slower than the contralateral, and of larger amplitude That there should be a difference is not perhaps surprising Certainly it must be argued that in the control of deviation the two mechanisms concerned have a close functional similarity Nevertheless, that this should be complete is probably not to be expected

The foregoing explanation embodies the assumption of a certain sequence in the damage sustained by the two deviational mechanisms within the brain stem, the view being taken that the more caudally situated vestibular tonus elements are usually affected in advance of the voluntary deviational elements Clearly, it is necessary to expect that a certain departure from the normal anatomy of an acoustic neurofibroma would bring about the reversal of this sequence Thus, a tumor with *an unusual upward* development would damage the voluntary deviational elements in advance of the caudally placed vestibular tonus elements The result of this would be a preponderance of ipsilateral nystagmus

A full description is given in the Appendix of two such cases In both a preponderance of ipsilateral nystagmus was correlated with the operative finding of brain stem involvement at an unusually *high* level

The role of cerebellar mechanisms

In what has been said of the neurological *mechanism* of the spontaneous nystagmus of *an* acoustic neurofibroma attention has been confined to the motor aspects of eye deviation control To this it need hardly be added that important subsidiary mechanisms are also likely to be involved

Thus in the normal *subject*, a very exact control of deviation is produced through the reflex *mechanism* of foveal fixation, which has recently been studied with such *precision* by Ditchburn (1955) and his co-workers

In the normal subject, too, good control of voluntary eye deviation is possible in the absence of visual fixation through the operation of the proprioceptive mechanisms of the extra ocular muscles

The importance of these subsidiary mechanisms is particularly well illustrated in the case *of a* typical canal imbalance nystagmus which im-

mediately follows a unilateral VIII nerve section. Here, if active visual fixation be permitted, than a very brisk nystagmus can be suppressed. In this situation, of course, the subsidiary mechanisms are intact.

By contrast, however, their derangement in the neurological stage of an acoustic neurofibroma is inevitable and this must accordingly be a factor of importance in the nystagmus which then occurs. As to the neurological basis of this derangement, it seems clear that for their proper working the subsidiary mechanisms in question must depend upon a measure of cerebellar control exercised through cerebellofugal pathways.

The pathways in question must traverse the closely crowded zone of the brain stem which has been affected by the tumor and are thus themselves subject to functional derangement.

In this sense, therefore, it would seem proper to say of the spontaneous nystagmus of an acoustic neurofibroma that in part at least it may be of cerebellar origin.

APPENDIX

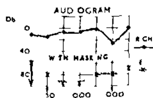
Case No. 1. G. S. aet. 60. I. P. Dr. Bannister.

The patient was admitted on 18th February 1961 to the National Hospital with a history of deafness and tinnitus of the left ear for the preceding four months. The patient also complained of recurrent attacks of vertigo precipitated by head movements. For the last eight months she had also noted a sensation of pins and needles in the left upper lip.

Neurological examination revealed a reduction of the left corneal reflex with blunting of sensation for pin prick over the first and second divisions of the left Vth nerve. Nystagmus was also present. X-rays of skull and temporal bones were normal.

Otological examination. Nothing abnormal was to be seen on examination of the ears, nose and throat.

Cochlear function. *Right.* Normal apart from slight deafness limited to the hearing for the frequency 4000 c/s. *Left.* Very severe deafness was present. This was of the perceptive type with incomplete recruitment of loudness. (See audiogram.)



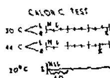
Vestibular function. The patient stood and walked very unsteadily with the eyes closed. Spontaneous 1st degree vestibular nystagmus was present with gaze to left and right. It was considerably more marked to the left than to the right.

Nystagmographic examination showed the nystagmus to be of the so-called central or deviation maintenance type.

Positional nystagmus. In the supine position with the head to left or right no change was observed of the spontaneous nystagmus.

Optokinetic nystagmus Responses were present both to left and right, with slight directional preponderance to the left

Caloric responses The right responses were normal The left responses were abolished



COMMENTS AND DIAGNOSIS

The otoneurological abnormalities were considered to indicate a gross lesion of the left VIIIth nerve with involvement of the brain stem elements which subserve conjugate deviation of the eyes to left and right Although the left sided deafness and the abolition of the left caloric responses made it clear that the left VIIIth nerve was affected the atypical direction of the preponderant nystagmus was a notable feature and was *thought to be indicative of a rather highly* placed tumor

Additional investigations X rays of the skull showed an area of translucency at the apex of the left petrous bone There was no expansion of the left internal auditory meatus

C S F protein 160 mg % Ventriculography showed deformity and displacement to the right of the IVth ventricle by an expanding lesion in the left cerebello pontine angle

Operative findings 2 4 64 Excision of left acoustic neuro fibroma by Mr McKissock A notable feature of the tumor was its upward extension *its large upper* pole being found to have passed beyond the tentorial hiatus

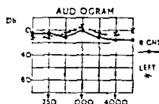
Case No II N H aet 22 I P Dr Denis Williams

The patient was admitted with a three months history of recurrent mild occipital headaches and two episodes of transient vertigo There was no complaint *of deafness but* occasional clicking sensations had been noticed in the right ear

Neurological examination revealed nystagmus on lateral gaze and possible impairment of right *corneal reflex*

Otological examination The corneal reflexes appeared to be equal and brisk *There* was a suggestion of weakness of the lower part of the right side *of the face but* this finding was difficult to interpret in the presence of some old facial scarring *There* was no inco-ordination of the hands Nothing abnormal was to be seen on *examination of* the ears nose and throat and there was no history of old *ear disease* deafness or tinnitus Tests *of* cochlear function showed normal hearing for the whispered voice Pure tone audiometry Normal apart from an extremely small loss for the right ear limited to the hearing for the frequency 8000 c s

Vestibular function The patient stood steadily with his eyes closed but deviated slightly *to the right* on walking with the eyes closed Spontaneous 1st degree vestibular nystagmus was present both to left and right It was considerably more marked to the *right* than to the left

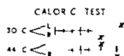


Nystagmographic examination showed the spontaneous nystagmus to be of the central or deviation maintenance type typical of an organic affection of the oculo versive elements within the brain stem

Positional nystagmus In the supine position with the head to left or right no change was observed in the spontaneous nystagmus

Optokinetic nystagmus Brisk responses were observed to the right at all speeds of the drum, responses to the left were virtually suppressed

Caloric test All responses were brisk and showed a well marked directional preponderance to the right



COMMENTS AND DIAGNOSIS

The otoneurological abnormalities in particular the central type of spontaneous nystagmus were thought to be indicative of an organic affection of the brain stem involving the mechanisms which sub serve conjugate eye deviation to left and right Although the general pattern of the spontaneous nystagmus closely resembled that usually found in the neurological stage of a *left* acoustic neuro fibroma this was certainly contra indicated by the finding of virtually normal hearing

Additional investigations X rays of skull and petrous temporal bones were normal C S F protein 110 mg % V E G showed displacement to left of the 4th ventricle by a space occupying lesion in the right cerebello pontine angle

Operative findings 29 10 64 Right posterior fossa exploration by Mr McKissock A large *right* acoustic neurofibroma was found with considerable extension upwards through the tentorial hiatus

Note In this case the tumor was a very unusual one extending upwards with very little damage to either the cochlear or vestibular elements of the right VIII nerve It *had* affected the voluntary eye deviation mechanism at a high level of the right side of the brain stem Hence the preponderance of the spontaneous nystagmus to the right

ACKNOWLEDGMENTS

Acknowledgments for permission to reproduce Figure 1 are made to the Editor of *Brain* Figures 2 3 6 and 7 to the Honorary Editors of the *Proceedings of the Royal Society of Medicine* Figures 8 and 10 to the Editors of the *Transactions of the Ophthalmological Societies* Figure 11 to Messrs Harper & Row Inc New York

ZUSAMMENFASSUNG

1 Es werden die Resultate einer Untersuchung auf spontanen Horizontal Nystagmus beschrieben der sich bei 75 Patienten mit einseitigem Akustikus Neurofibrom fand

2 Aus Gründen der besseren Übersichtlichkeit wurden alle Tumoren des rechten Nerven als solche des linken Nerven angesehen gleichzeitig wurde auch eine entsprechende Seitenumkehr des Nystagmus und der anderen neurologischen Symptome vorgenommen Es ergab sich dadurch eine Gesamtzahl von 75 Patienten mit linksseitigem Tumor

3 Der Nystagmus wurde entsprechend der herkömmlichen Bezeichnungsweise nach Richtung und Intensität eingeteilt

4 Bei vielen Patienten war ein Nystagmus sowohl nach rechts wie auch nach links vorhanden Bei diesen wie auch bei anderen Patienten bestand ein eindeutiges Überwiegen des Nystagmus nach rechts

5 Eine elektronystagmographische Analyse des Spontan Nystagmus wurde bei einer Reihe typischer Fälle durchgeführt Im Gegensatz zu den Befunden nach einseitiger Destruktion des N VIII oder des Labyrinthes ergab sich daß der Nystagmus durch Ausschaltung der visuellen Fixation gehemmt wurde und zwar sowohl durch Dunkelheit wie durch Lidschluß mit einer Rückkehr der Augen aus ihrer Deviationsstellung zu einer Ruhestellung näher der Geradeaus Richtung Wenn jedoch unter Ausschluß der visuellen Fixation die Augendeviation in Richtung des eigenen Daumens des Patienten mit Hilfe proprioceptiver Mechanismen aufrechterhalten wurde blieb der Nystagmus bestehen wenngleich mit einer gewissen Verminderung seiner Frequenz und seiner Regelmäßigkeit

6 Im Hinblick auf die Feststellung daß der Nystagmus nicht abhängig war von der Fixation an sich oder von anderen visuellen Mechanismen sondern eher von der Aufrechterhaltung der konjugierten Augendeviation wird der Vorschlag gemacht ihn zu definieren als Deviations Erhaltungs Nystagmus

7 Der Nystagmus wird als Folge einer Schädigung angesehen die durch den Tumordruck an bestimmten Hirnstamm Mechanismen entsteht die mit der Kontrolle der konjugierten Augenbewegungen in der Horizontalebene zu tun haben

Ein solcher Mechanismus ist jener der vestibulären Tonus Elemente von dem man glaubt daß er caudal innerhalb des Vestibularis kern Komplexes gelegen ist Der Tumordruck neigt dazu diese frühzeitig zu beeinflussen und ist die Ursache des Deviations Erhaltungs Typs des Nystagmus nach rechts

Der zweite Mechanismus ist jener der die spontane konjugierte Augendeviation nach links betrifft Wie von Bender beschrieben befinden sich die neuralen Elemente die diesem Mechanismus dienen auf der linken Seite des Hirnstammes oberhalb des Niveaus der Vestibularis kerne Der Tumordruck pflegt sie etwas später zu beeinflussen als die vestibulären Tonus Elemente und ist die Ursache des Deviations Erhaltungs Typs des Nystagmus nach links

Man glaubt daß die Schädigung anderer Hirnstamm Mechanismen eine bestimmte jedoch untergeordnete Rolle in der Entstehung des Spontan Nystagmus spielt Diese schließen die retikulären Komponenten ein von denen bekannt ist daß sie mit den vestibulären Elementen vereinigt sind und auch die zahlreichen cerebellären Afferenzen zu den vestibulo-oculären und oculo motorischen Systemen

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NEUE WEGE DER TYMPANOPLASTIK

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Im Platin- und Golddraht von 0,2 bis 0,3 mm Durchmesser steht uns zur Ueberbrückung von Defektstrecken und zum Ersatz funktionsuntüchtiger Gehörknöchelchenabschnitte ein Material zur Verfügung, dem schnell die erforderliche Form gegeben werden kann und das wahrscheinlich genauso gut verträglich ist wie PVC-Kunststoffe und implantiertes körpereigenes Gewebe. Anhand von Skizzen wird eine Reihe von Defektsituationen demonstriert, in denen mit Hilfe dieser Edelmetallbrücken die Schallübertragung optimal wiederhergestellt werden kann. Der große Vorteil dieser Methode liegt in der Möglichkeit der ausgezeichneten Fixierung, die auch Entzündungsrezidiven mit starker Sekretion oder mechanischen Erschütterungen durch Luftduschen oder andere Ursachen ausgezeichnet standhält. Ob ich beim Einbau der Drahtkonstruktionen endaural vorgehe oder retroauriculär, muß von Fall zu Fall entschieden werden. Wie wir anhand einer Reihe von durchgeführten Operationen zeigen konnten, hat sich uns die vorgeschlagene Methode bisher gut bewährt. Eine kritisch-statistische Auswertung unserer Ergebnisse ist jedoch noch nicht möglich. Die Ausführungen sollen in Form eines vorläufigen Berichts zum Erfahrungsaustausch anregen.

Durch die wegweisenden Arbeiten von Kessel (1878), *Moritz* (1950–51), *Wullstein* (1949, 1952, 1961), Zöllner (1958, 1960, 1963) und Heermann & Heermann (1964) sind die restaurierenden Eingriffe am Mittelohr in ihren *Grundzügen* festgelegt. Das Ziel des mikrochirurgischen Vorgehens im Mittelohr ist neben *der Sanierung* entzündlicher Prozesse die möglichst optimale Gestaltung *der Schalldrucktransmission*. Um eine gute Übertragung der *Schallenergie zu* erreichen, wird es *erforderlich* sein, funktionsuntüchtige Schallstrecken auszuschalten und durch schwingungsfähige Gebilde zu ersetzen. Ebenso sind Defektstrecken *durch* mechanische Energieüberträger zu überbrücken.

Während *man* viele Jahre hindurch die Schallbrücken aus Naturbausteinen (Knorpel, Knochen und Bindegewebe) *formte*, wird die Verwendung von Kunststoffen (PVC und *Polyäthylen*, Teflon) immer ernsthafter diskutiert. Den *Kunststoffen* nähern sich Konstruktionen aus Tantaldraht, wie sie z. B. von Schuknecht (1960), Portmann (1962) und Plester (1959) als Steigbügelersatz durchgeführt *werden*. *Schubert* (1964) verwendet eine goldene Fußplatte mit Verbindungsdraht zum Amboßschenkel, wodurch

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Angesichts der guten Erfahrungen, die Schuknecht (1960), Portmann (1962) und Plester (1959) beim Stapesersatz durch Draht aufzuweisen hatten, prüften wir dieses Material auch auf seine Verwendungsfähigkeit bei Tympanoplastiken, und zwar einerseits bei relativ reizlosen Mittelohren (Amboßverlust nach Antrotomie, Gehörknöcheldefekte nach Schädeltraumen) und andererseits bei verschiedenen Stadien chronischer Schleimhaut- oder Knocheneiterungen. Im Draht haben wir ein Bauelement kennengelernt, das, was die funktionell sichere Verankerung betrifft, allen anderen Bausteinen überlegen ist. Nicht umsonst spielt der Draht schon seit der Mitte des 19. Jahrhunderts (Patellanaht) eine so wichtige Rolle in der allgemeinen Chirurgie, und zwar besonders deshalb, weil er so zuverlässige Fixierungen ermöglicht.

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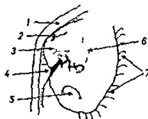


Abb 1 Abb 2

Abb 1 Drahtgitter zur Stutzung des Transplantates bei großer Trommelfellperforation

Abb 2 Kleine Amboß Steigbugelbrucke bei fehlendem Proc lenticularis nach Schadel trauma 1) N facialis 2) Fußplatte 3) Steigbugel 4) Proc pyramidalis + Sehne des Musc stapedius 5) Nische zum runden Fenster 6) langer Amboßschenkel 7 nach vorn geschlagenes Trommelfell (endaurales Vorgehen)

Den Abb 2 4 5 6 10 12 14 und 16 liegt die gleiche Grundskizze zugrunde

werden (Abb 2) Eine solche Situation liegt dem Audiogramm der Abb 3 zu grunde Der 38jahrige Patient (W J) erlitt 1955 einen Motorradunfall mit Blutung aus dem linken Ohr Es wurde damals eine hochgradige Mittelohr schwerhorigkeit links festgestellt die sich in der Folgezeit nicht besserte Auf grund unserer Impedanzprufungen vermuteten wir eine traumatische Unter brechung der Gehorknochelchenkette, die sich bei der Operation vor sechs Mo naten als isolierter Defekt des Processus lenticularis bestatigte Die obere Luft leitungskurve wurde durch eine A S Brucke aus Golddraht (0 2 mm Ø) erreicht Bei großeren Defekten des langen Amboßschenkels ist sinngemaß eine große A S Brucke einzubauen (Abb 4)

Ist der Amboß infolge Verwachsungen die auch nach Lösung schnell wieder eintreten oder durch Totaldefekte des langen Schenkels nicht mehr als Uber tragungsglied zu verwerten muß eine Brucke vom Hammer und zum Steigbugel geschlagen werden (HS Brucke = kunstlicher Amboß) Nach Abpraparieren des

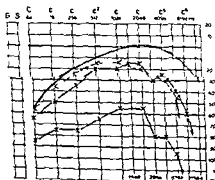


Abb 3



Abb 4

Abb 3 (W J., 38 J., ♂) Isolierter Defekt des Proc lenticularis

Abb 4 Großere Amboß Steigbugelbrucke

ment gegen die Verwendung von Schallbrücken aus Draht vorzubringen ist wäre es nicht zu verstehen, wollte man nicht das Material verwenden, das die besten funktionellen Eigenschaften aufweist In Anbetracht der guten Erfahrungen mit Edelmetallen auch auf anderen Gebieten schlagen wir deshalb vor, zur Konstruktion eines möglichst optimalen Schwingungssystems im Mittelohr Draht oder Streifen aus Gold (24 Karat) oder aus reinem Platin zu verwenden Soweit es die Ausschaltung eines Cholesteatoms, die Schleimhautverhältnisse (nicht mögliche Entepidermisierung der medialen Paukenhöhlenwand) oder die Tubensituation zulassen, sollte der Aufbau einer weiten Pauke mit günstiger Trommelfellfläche ermöglicht werden Das Fehlen des Steigbügels, des Ambosses oder des Hammers oder das Fehlen aller drei Gehörknöchelchen allein ist noch kein Grund, eine Plastik des Typ IV durchzuführen Wie wir zeigen werden, besteht in Abhängigkeit von der klinischen Situation die Möglichkeit der Rekonstruktion einer geschlossenen Paukenhöhle mit funktionierendem Schwingungssystem, wenn wir entsprechend unserem Vorschlag Draht aus Gold oder Platin (0,2–0,3 mm stark) oder 0,2 mm starke und 2 mm breite Gold- oder Platinstreifen verwenden

Das gute Funktionieren dieser Schallbrücken wird durch unsere ersten Erfahrungen bestätigt Da hier Neuland betreten wird, können wir allerdings noch keine langzeitigen Verlaufsbeobachtungen mitteilen Somit kann unsere Publikation bezüglich der Aufbausituationen in chronisch-entzündlich veränderten Mittelohren vorerst nur den Charakter einer vorläufigen Mitteilung haben, die zu einem Erfahrungsaustausch anregen soll Was jedoch unsere Erfahrungen mit Rekonstruktionen des Mittelohres bei relativ reizlosen Verhältnissen betrifft (iatrogene oder traumatische Schädigungen des Mittelohrapparates), so haben sich die Schallbrücken aus Edelmetall bereits über ein Jahr und länger bewährt Gerade bei chronischen Knochen- oder Schleimhauteiterungen, Adhäsionsprozessen oder traumatischen Defektbildungen sind die jeweiligen pathologischen Situationen so vielgestaltig, daß sich der Phantasie und dem Geschick des Operateurs ein weites Feld restaurierender Möglichkeiten eröffnet So soll im folgenden kein lückenloses Bild von Aufbausituationen gezeigt werden Wir möchten nur einige uns bewährte Konstruktionsvorschläge zur Diskussion stellen

1) Bei ausgedehnten *Trommelfell Perforationen* ist oft trotz entsprechender Geräumigkeit des Paukenkellers und zur Vermeidung des Verwachsens mit dem Promontorium eine Stütze des Haut oder Sehnentransplantates vorteilhaft Wie in Abb 1 dargestellt, kann man je nach Größe des Trommelfelldefektes das zarte Drahtgitter variieren und erreicht damit einen guten Abstand zwischen dem neuen Trommelfell und der medialen Paukenhöhlenwand Funktionell paßt sich die feine Drahtverspannung infolge des optimalen Elastizitätsmoduls ausgezeichnet an

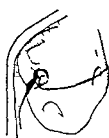
2) *Amboßdefekte* Eine kleine Amboß Steigbügel Brücke (A S Brücke) kann bei Verlust des Processus lenticularis des langen Amboßschenkels notwendig



Abb. 9. Künstlicher Amboß im Röntgenbild nach Stenvers

Druck auf den Steigbügel bzw. auf die Fußplatte kontrolliert werden können (Wechseltakt nach Wullstein 1949, 1952, 1961). Das Audiogramm (Abb. 8) demonstriert eine solche HS-Brücke. Bei dem 27jährigen Patienten (Z. V.) war es im Volksschulalter nach Antrotomie rechts zu einer hochgradigen Schwerhörigkeit rechts gekommen. Da der Patient als Verkaufsleiter sehr auf binaurales Hören angewiesen war, kam er in unsere Klinik mit der Frage, ob sich das Gehör rechts wieder herstellen ließe. Bei der Operation vor acht Monaten fand sich kein Amboß mehr vor. Da wir die Brücke, wie bereits beschrieben, locker einpassten, kam der volle Hörgewinn erst 14 Tage nach der Operation zustande.

3) *Steigbügel und kombinierter Steigbügel-Amboß-Ersatz*. Fehlt der Steigbügel oder ist er infolge rarefizierender Prozesse nicht mehr funktionstüchtig, so ist von der Fußplatte oder gegebenenfalls vom Fenstertransplantat über dem ovalen Fenster eine Verbindung zum intakten oder defekten Amboßschenkel herzustellen (Abb. 9). Dem Audiogramm (Abb. 10) (I. H., 35 J.) liegt ein Zustand bei Adhäsivprozess mit klinischer Otosklerose zugrunde. Der Drahtsteigbügel liegt dem Fenstertransplantat auf und ist fest am langen Amboßschenkel fixiert. Hier war zunächst ein Polyäthylenröhrchen eingesetzt, das aber schon nach wenigen Tagen bei heftigem Schneuzen disloziert wurde infolge Druckwelle im Mittelohr durch die Ohrtrompete. Bei der Nachoperation fand sich das Röhrchen im Paukenkeller. Jetzt nach sieben Monaten ist das Gehör gut geblieben, obwohl der Patient mehrmals am Tage seine Pauke mit Hilfe des Valsalvaschen Versuchs belüften muß.



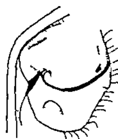


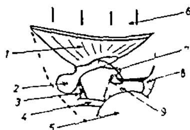
Abb. 5 Abb. 6

Abb. 5. Hammer-Steigbügelbrücke (künstl. Amboß) aus Draht.

Abb. 6. Hammer-Steigbügelbrücke aus Metallstreifen.

Trommelfelles vom Hammerstiel 1–2 mm oberhalb des Umbos wird ein Draht hier um den freigelegten Hammerstiel geschlungen. Das untere Drahtende wird *unter* der Stapediussehne hindurch um den Steigbügelkopf gelegt. Bei der Mobilisation des Trommelfelles ist eine Perforation des Trommelfelles leicht zu vermeiden, man muß sich mit dem gebogenen Flachmesserchen nur dicht am Hammerstiel halten (Abb. 5). In Abb. 6 wird die gleiche endaurale Situation mit Edelmetallstreifen um den Hammerstiel gezeigt. Sowohl Draht als auch Streifen brauchen nicht zu Druckusuren zu führen. Eine lockere Führung um den Hammerstiel und Steigbügelkopf ist funktionell und für die Fixierung ausreichend, da schon nach ein bis zwei Wochen Gewebskontakt eintritt. Bei atrophischen zerreißlichen Trommelfellen halten wir ein retroaurikuläres Vorgehen in Form einer Attico-Antrotomie für verläßlicher.

Abb. 7 zeigt den guten Einblick in die Pauke. Bei entsprechender Kopfdrehung ist auch das runde Fenster einzustellen, so daß die Perilymphbewegungen bei



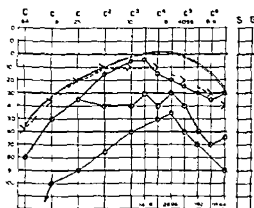


Abb. 7 Abb. 8

Abb. 7. Hammer-Steigbügelbrücke von der Attico-Antrotomie aus. 1. Trommelfell-Trichter, 2) Hammer, 3) Proc. cochleariformis mit Tensor tympani, 4) N. facialis, 5. horizontaler Bogengang, 6) hintere knöcherne Gehörgangswand, 7. Drahtbrücke (künstl. Amboß), 8) Proc. pyramidalis mit Stapediussehne, 9) Steigbügel.

Abb. 8. (Z. V., 27 J., ♂.) Amboßverlust nach Antrotomie (günstigste Luftleitungskurve 1 Jahr nach Operation).



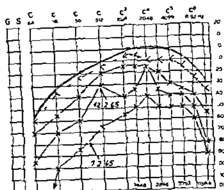


Abb 14

Abb 15

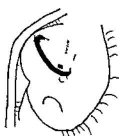
Abb 14 Zwei oder mehrschenklige Brücke vom Steigbügel zum Trommelfellrand bei Hammer- und Amboßverlust und großer Trommelfellperforation

Abb 15 (D G., 26 J ♂) Audiogramm zur Situation der Abb 14 Optimale Luftleitungskurve ist Endresultat

Durchblasegeräusch beobachtet sondern wölbt sich nur die Pars tensa vor (zusätzliche Prüfung unter dem Ohrmikroskop oder unter der Lupe!), so ist nach Zange ein narbiger Abschluß des Kuppelraumes gegen das Mesotympanon zu erwarten der bei der Operation unbedingt zu erhalten ist Eine Paukenkontrolle erübrigt sich dann da nicht zu befürchten ist daß sich das Cholesteatom in den abgeschlossenen Paukenraum fortgesetzt hat

Im beschriebenen Fall (K R) hatte sich erwartungsgemäß das Cholesteatom in den hinteren Paukenraum vorgeschoben und zur Zerstörung des langen Amboßschenkels und der Steigbügelschenkel geführt Glücklicherweise ließ sich der in die Paukenhöhle eingedrungene Cholesteatomsack als Ganzes fassen und vollkommen entfernen Deshalb war der Einbau einer großen Drahtbrücke von der beweglichen Fußplatte zum partiell skelettierten Hammergriff zu verantworten Die völlig erhaltene Pars tensa mit Sourdillelappen schloß die Pauke wie der ab Der Hörgewinn ist aus dem Audiogramm abzulesen (Abb 13) Die Möglichkeit eines Einfügens einer Schallbrücke war hier deshalb besonders wertvoll da das andere Ohr bereits bei etwa gleichem Befund außerhalb in Form einer Radikaloperation mit totaler Ausweidung der Paukenhöhle operiert wurde, woraus eine hochgradige Schwerhörigkeit resultierte

4) *Amboß und Hammerverlust* Bei Amboß und Hammerverlust aber noch erhaltenem Steigbügel schlagen wir eine zweischenkelige Drahtbrücke vor wie sie in Abb 14 dargestellt ist Durch Ausbiegen der Schenkel läßt sich die Pauke auf etwa normale Weite bringen Die Abb 14 (Audiogramm) nimmt Bezug auf die Situation eines Patienten mit Trommelfell Totaldefekt der bei uns in der beschriebenen Weise operiert wurde Als operativer Zugang wurde der retroauriculäre Weg gewählt (Attico Antrotomie) Nach Abschieben des hinteren häutigen Gehörganges wurde daraus ein Trommelfell Transplantat herausgeschnitten und passend gemacht Durch die so entstandene Lücke im Gehörgangsschlauch



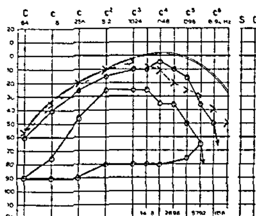


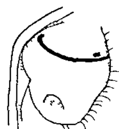
ABB. 10 ABB. 11

ABB. 10. Amboß-Fußplattenbrücke.

ABB. 11. Amboß-Fenstertransplantat-Brücke bei Adhäsivprozeß. (Oberste Luftleitungskurve gibt operativen Hörgewinn gegenüber unterster Luftleitungskurve an.)

Fehlen nicht nur die Steigbügelschenkel, sondern auch der Amboß, so wird eine große Fußplatten-Hammer-Brücke konstruiert (Abb. 12). Als klinisches Beispiel ein primäres Cholesteatom bei einem 17jährigen Jungen (K. B.): typischer Shrapnelldefekt, beim Politzern Durchblasen von eitrigem Sekret durch die Perforation. Dieses Zeichen sprach dafür, daß zwischen Epitympanon und Mesotympanon kein narbiger Abschluß bestand, worauf auch der große Hörverlust in der Luftleitung hinwies. Es war also ein Kuppelcholesteatom mit Übergreifen auf das hintere Mesotympanon mit Zerstörung im Amboßbereich zu erwarten trotz der völlig erhaltenen Pars tensa.

Deutet der Verlauf der Luftleitungskurve nicht auf eine Unterbrechung der Schalleitungskette und wird bei primärem Cholesteatom beim Politzern kein



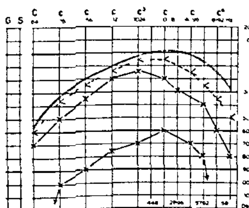


ABB. 12 ABB. 13

ABB. 12. Große Hammer-Fensterplattenbrücke bei erhaltener Pars tensa.

ABB. 13. Große Hammer-Fußplattenbrücke bei primärem Cholesteatom mit Zerstörung von Amboß und Steigbügel, aber erhaltener Pars tensa. (Oberste Luftleitungskurve 6 Monate nach Operation.)



Abb 14

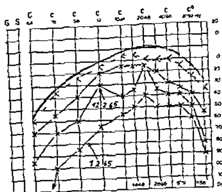


Abb 15

Abb 14 Zwei oder mehrschenklige Brucke vom Steigbugel zum Trommelfellrand bei Hammer und Amboßverlust und großer Trommelfellperforation

Abb 15 (D G 26 J ♂) Audiogramm zur Situation der Abb 14 Optimale Luftleitungskurve ist Endresultat

Durchblasegerausch beobachtet sondern wolbt sich nur die Pars tensa vor (zusatzliche Prufung unter dem Ohrmikroskop oder unter der Lupe!) so ist nach Zange ein narbiger Abschluß des Kuppelraumes gegen das Mesotympanon zu erwarten der bei der Operation unbedingt zu erhalten ist Eine Paukenkontrolle erubrigt sich dann da nicht zu befurchten ist daß sich das Cholesteatom in den abgeschlossenen Paukenraum fortgesetzt hat

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Abb. 16. Aufbau eines Paukengerüstes bei Verlust aller Gehörknöchelchen und Trommelfelltotaldefekt. Die Drahtkonstruktion dient dem Trommelfell-Transplantat als Stütze.

läßt sich nun zusätzlich ein weiter Trichter einführen, der eine gute Übersicht über den Trommelfellbereich erlaubt. Den Hörgewinn veranschaulicht unsere Abb. 15. Hier wurde Platindraht, 0,3 mm stark, verwendet. Der Lappen heilte gut ein. Die Attico-Antrotomie diente hier vornehmlich der Drainage, die wir bei Schleimhauteiterung, auch wenn schon gut sechs Monate keine Sekretion mehr bestand, für die ersten postoperativen vierzehn Tage für sehr wertvoll halten.

5) *Verlust aller Gehörknöchelchen.* Besteht für den künstlichen Steigbügel keine Möglichkeit, am Amboß oder am Hammer verankert zu werden, so stehen wir vor der Aufgabe, durch Streben eine solide Stützung vorzunehmen. Dabei können wir durch eine verlängerte Kolumella (5–6 mm lang) aus Edelmetalldraht mit herausgebogenen Streben gleichzeitig eine Vergrößerung des Paukenraumes erreichen (Abb. 16). Am zweckmäßigsten stützt sich eine Strebe auf den Bereich des horizontalen Bogenganges, und zwei weitere werden am hinteren und mittleren unteren Trommelfellrahmen aufgesetzt. Bei binauralem Arbeiten, wofür sich bei allen endauralen Eingriffen besonders die Heermannsche Methode bewährt hat, wird auch diese Drahtkonstruktion in die erforderliche funktionelle optimale Lage gebracht werden können. Dabei erhält auch das in diesen Fällen fast immer notwendige Trommelfelltransplantat eine ausreichende Stütze.

SUMMARY

In platinum and gold wire of 0.2–0.3 mm diameter there is a material available for bridging and substituting sections of the ossicular chain with inefficient function. This material can readily be formed as needed and may be regarded at least as tolerable as PVC and implanted tissue. Some sketches of defect situations are demonstrated in which by bridging with such precious material optimal sound transformation may be restored. The great advantage of this method is the possibility of good fixation withstanding inflammation recidives and mechanical concussion by tympanic inflation or other causes. Whether the construction is installed endorally or retroorally has to be decided on according to circumstances. As we were able to demonstrate this method was quite a success in the operations performed. As yet a critical analysis by statistics has not been possible. This paper is meant to be a first report in order to induce an exchange of experience.

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STUDIES ON PROGRESSIVE HEREDITARY PERCEPTIVE DEAFNESS IN A FAMILY OF 335 MEMBERS

I Genetical and General Audiological Results

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Progressive hereditary perceptive deafness has been studied in a family of 335 members in 5 generations with the following results (1) The inheritance of the deafness in this family is of the autosomal dominant type with complete penetrance (2) The deafness is a symmetric pure perceptive hearing loss affecting high frequencies first and most seriously (3) The hearing impairment proceeds rapidly in the first 3 decades to 60 70 dB whereafter the progression slows down (4) The progression of the hearing impairment follows a distinct pattern in which 5 characteristic stages are distinguished which are discussed in detail in a second article (5) Characteristic stages of threshold loss correlate with typical speech audiometric curves (6) Recruitment is present (modified monaural masking method) while difference limen of intensity is decreased (Sisi test) perstimulatory adaptation is normal (tone decay test)

INTRODUCTION

A study of progressive hereditary perceptive deafness was carried out in a family of 335 members in 5 generations The pattern of inheritance was examined and the nature of the deafness and its progression investigated This article deals with the genetical and general audiological results of the study In a second article the pattern of progression of the deafness is discussed and an attempt is made to correlate the degeneration pattern to some recent observations on cochlear architecture and function

Albrecht (1922) was the first to recognise progressive hereditary perceptive deafness as a clinical entity when he established that its inheritance was dominant This in contrast with congenital hereditary perceptive deafness which is a recessive trait The dominancy of the inheritance has been confirmed since by Popow (1935) Schneider (1937) Stephens & Dolowitz (1949) and Johnsen (1952) However Johnsen (1954) and Cawthorne

& Hinchcliffe (1957) have also described cases in which the inheritance pattern seemed to be recessive

Although audiological studies on progressive hereditary perceptive deafness are scarce it appears that a symmetrical high tone loss with a rather steep slope in the audiogram is the most frequent type of hearing impairment that has been found In some cases, however, basin-shaped and ascending audiometric curves have been observed De Bruïne-Altes (1946) found recruitment in all her cases whereas Dolowitz & Stephens (1961) found none The progressive character of the deafness, which was implied by all the authors mentioned, has never been described in any detail, but it seems to be the only constant observation

APPARATUS AND PROCEDURE

Audiograms for both ears were made by means of a van Dishoeck sweep frequency audiometer (Peekel D 4) Sweep frequency audiometry is of particularly great value when accurate and fast determinations of the slope of the audiometric curves are required This audiometer was adapted for (1) speech audiometry with P B lists, (2) recruitment measurements by means of a modified monaural masking technique, (3) SISI test (Jerger), (4) tone decay test

In the towns or villages where members of the family were living, a test-room was chosen with an ambient noise level as low as possible Due to the still present masking interfering noise, a low tone threshold shift of 10–20 dB was found

Since the hearing loss in early stages was mainly for high tones the presence of masking noise did not interfere with the threshold measurements for frequencies above some 1000 Hz

Before testing a routine case history was taken, followed by otological examination 258 out of the 335 members of the family were tested For different reasons, e g death and emigration, only anamnestical data could be collected about the others

1 *Genetical Results*

The family under investigation consisted of 335 members divided among five generations The original parent had 6 children, and so 6 main branches can be distinguished in the pedigree In total 67 members of the family appeared to be suffering from the progressive perceptive deafness In 58 cases the diagnosis was made from the audiological results in 7 cases it was concluded from the anamnestical data

Fig 1 shows the pedigree of the family and the occurrence of the progressive perceptive deafness among its members It is apparent that the disease is frequent in the branches 2, 3 and 6 in which the original parent (I_1) is affected In the branches 1, 4 and 5 on the contrary, in which the original parent (I_1) has normal hearing, nobody is affected

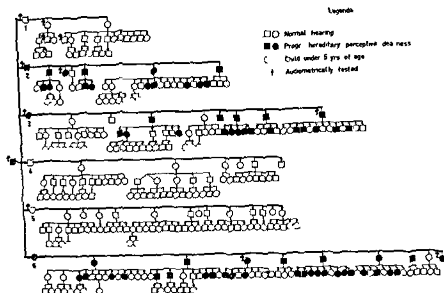


FIG 1 Pedigree of the family deafness is present in branches of affected ancestors only

Children under the age of five are *indicated differently in the pedigree* as no manifestation of the disease was detected below this age There were no marriages between members of the family Among the in law relations no hereditary deafness could be established

In branch 6 a congenital pendulary nystagmus of retinal origin was found in five male members The presence of this nystagmus was not combined constantly with the deafness Other hereditary abnormalities were not detected

The pedigree shows that all normal hearing members of the family have normal hearing children This holds for the unaffected branches as well as for the branches 2 3 and 6 where the disease is present The affected members have normal hearing as well as affected children The ratio be tween the normal hearing and the affected direct descendants of all af fected persons in F_1 F_2 and F_3 together amounts to ca 1 1 (Table 1)

It follows therefore that the inheritance of the trait in this family too is of dominant type with complete penetrance There *is no sex linkage,* as 38 of the 67 affected members are male and 29 are female These findings

TABLE 1 *The number of affected and normal hearing direct descendants of all affected persons in F_1 F_2 and F_3*

	Affected	Normal
F_1	3	3
F_2	18	5
F_3	67	66

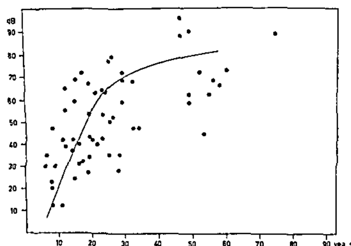


Fig. 2. Mean perceptive hearing loss for 500, 1000 and 2000 Hz as a function of age, note rapid increase of hearing loss in the first 3 decades.

are in accordance with the observations of other authors (Albrecht, Schneider, Stephens & Dolowitz).

2. *General Audiological Results*

All 58 of the 67 affected members of the family who could be tested showed a symmetrical perceptive deafness. In early cases the hearing impairment concerned high frequencies only. In more advanced cases low tones are also affected although to a smaller extent than the high frequencies.

The degree of the hearing loss was closely correlated with age. Fig. 2 shows the mean perceptive threshold loss at 500, 1000 and 2000 Hz as a function of age. The hearing loss appears to proceed rapidly in the first three decades, the mean hearing loss at the age of about 25 years amounting to 60–70 dB. The progression then apparently slows down since the mean hearing impairment at 40–60 years of age differs only slightly from the loss at the age of 25–30 years. Hearing loss was not found to be apparent in children under 5 years of age. From the sweep frequency audiograms it appeared that the progression of the hearing impairment in this family *followed a constant pattern. Five characteristic stages A–E can be distinguished.* They are shown in Fig. 3. These audiometrical stages of progression will be described and discussed in detail in a second article.

Speech audiometry consisted of presentation of P.B. lists of 20 monosyllabic and disyllabic words. There is a correlation between the stage of threshold loss and the type of speech audiogram. Speech audiograms of type A (Fig. 4) are found in cases in which the hearing impairment is that of Stage A or less. With further progression of the deafness with pure tone audiograms of Stage B and sometimes of Stage C, the curve of speech intelligibility shifts more to the right and a discrimination loss occurs.

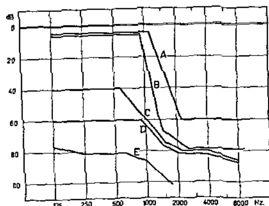


Fig 3 Characteristic audiometrical stages of progression of the hearing impairment

(curve B Fig 4) *In still more advanced cases with pure tone audiograms* of Stages C and D a helmet shaped curve was found (curve C Fig 4) Curve D corresponds with Stages D and E

Recruitment was investigated by means of a special monaural masking method For this purpose the original monaural masking technique as described by Huizing Sr (1942) and de Bruine Altes & Huizing Sr (1949) was modified Two sweep frequency audiometers are used The first audiometer proceeds a continuous *masking tone* (M T) the second one gives a pulsating *test tone* (T T) Both tones are delivered to the same ear

As test tone a frequency is used at which one wishes to investigate the presence of recruitment As masking tone a frequency is chosen at which threshold is normal and which is as near as possible to the test tone in order to obtain the greatest masking effect Any harmonic relation between the two tones has to be avoided The threshold of the test tone is now measured at different intensity levels of the masking tone Normally the

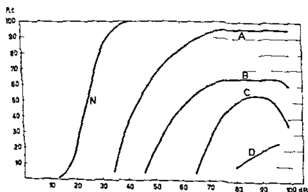


Fig 4 Typical speech audiograms corresponding to the characteristic Stages A D of the pure tone audiograms

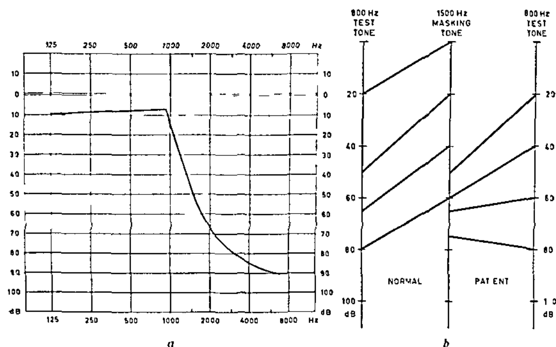


Fig. 5 *a* and *b*. Monaural masking test showing recruitment in a number of the family with a characteristic audiogram.

threshold of the test tone will increase proportionally to the increase of the intensity of the masking tone. If recruitment is present, however, it will increase to a smaller extent. With this method the presence of recruitment was investigated in a number of cases with suitable audiograms. In all of them partial or complete recruitment was found. A typical example is demonstrated in Fig. 5 *a* and *b*.

Difference limen of intensity was measured in 10 cases according to the SISI test (Jerger, 1959). The results showed a distinct decrease of the difference limen of intensity as compared to normal.

Perstimulatory adaptation was measured in all cases by means of the tone decay test at a frequency at which threshold loss was moderate. Except in one subject in which adaptation was prolonged moderately, results were within normal limits.

ZUSAMMENFASSUNG

Die progressive hereditäre Innenohrschwerhörigkeit wurde untersucht in einer Familie von 335 Mitgliedern in fünf Generationen mit folgenden Ergebnissen: 1) Die Vererbung der Schwerhörigkeit ist autosomaldominant mit völliger Penetranz. 2) Die Schwerhörigkeit ist eine symmetrische reine Innenohrschwerhörigkeit, welche die hohen Töne in erster Linie angreift. 3) Der Hörverlust nimmt in den ersten drei Dekaden bis auf 60–70 db zu, wonach die Progression abnimmt. 4) Die Progression der Schwerhörigkeit hat einen typischen Verlauf, worin 5 charakteristische Stadien zu erkennen sind, worüber ein zweiter Artikel

erscheinen wird 5) Es gibt eine Korrelation zwischen den typischen tonaudiometrischen Stadien und den sprachaudiometrischen Kurven 6) Es liegt ein Lautheitsausgleich (geanderte monaurale Maskierungstechnik) vor die Intensitätsunterschiedsschwelle (SISI Test) ist verkleinert, die perstimulatorische Adaptation ist normal (tone decay test)

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CHOANAL POLYPS

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The author analyses 80 cases of choanal polyp. The material is from the Otolaryngological Hospital of the University of Helsinki from 1945 to 1958.

Benign polyps of inflammatory or allergic origin are common causes of nasal obstruction Much more infrequent and quite peculiar is the choanal polyp which has certain distinctive features of its own As this polyp grows larger it extends into the choana filling it completely and occasionally also the nasopharynx, which accounts for the name applied to the polyp

Palfyn was probably the first to describe, in 1753, a typical case of choanal polyp In the nineteenth century, removal of choanal polyps was already suggested in some reports (Sands, 1887, Lange, 1887) and hypotheses as regards their point of origin were put forward (Zuckerkandl, 1892) However, it was Killian (1906) who first published a thorough description of a greater number of cases studied in detail He traced the choanal polyp to the maxillary sinus and stated that its pedicle passes thence through the ostium into the middle meatus, the polyp extending further into the nasopharynx Choanal polyps, therefore, have often been termed Killian polyps The following designations have also been used nasoantral polyp, benign nasopharyngeal polyp, postnasal polyp, antrochoanal polyp, juvenile recurring polyp, solitary choanal polyp, and retronasal polyp All these names in some way describe this peculiar kind of polyp

Killian did not, however, report any intrasinus observations regarding the point of origin of the pedicle Since then, various observers have reported diverging views on this question (Kubo, 1909, Kelly, 1909, Syme, 1916, Ewing, 1918, Stawraski, 1928, Semenov, 1952) Kubo, in 1913, published a detailed report of his observations at maxillary sinus resections in 37 cases of choanal polyp In these cases the polyp stalk was traceable to some wall of the sinus, the most infrequent point of origin being the anterior wall and the roof of the cavity Semenov (1952) and Ash & Raum (1955) stated that the lateral wall is the most frequent site of origin, and it was very common in Kubo's series too They offered the

explanation that the mucosa in the lateral wall is thin and delicate so that the least disturbances cause it to become oedematous and polypoid because of the poor circulation and long lymphatic channels with resulting poor canalization of the mucosa

Choanal polyps have only seldom been traced to any site other than the maxillary sinus a few cases have been described in which a polyp arose from the sphenoidale sinus and from the posterior ethmoid cells (Kubo 1909 Syme 1916 Ewing 1918)

Numerous theories and assumptions have been presented on the mode of travel of the polyp from the sinus through the ostium to the nasal meatus and on its development to the final stage when it hangs out of the choana into the nasopharynx (Kelly 1909 Syme 1918 Ewing 1918 Forschner 1921 Hirsch 1927 and 1928 Stawraski 1928 von Baykay 1933 Dingley 1949)

Authorities are generally agreed that this polyp does not differ histologically from an ordinary nasal polyp It has been noted that the number of mucosal glands in the polyp differs according to its point of origin and that a polyp arising from the maxillary sinus contains larger glands than does the nasal mucosa (Ash & Raum 1955) In addition it has been claimed that eosinophilic cells are less numerous in a choanal polyp than in an ordinary nasal polyp (Semenov 1952 Heck Hallberg & Williams 1950)

The incidence figures reported for choanal polyps have varied widely According to Syme (1918) and Morwitz (1931) about 3 per cent of all patients with maxillary sinus disease have choanal polyps Syme s series of 393 patients treated by radical maxillary operation included 26 cases of choanal polyp (6 6 per cent) and two of these were bilateral Mithoefer (1926) estimated that 12 5 per cent of all surgically treated cases of maxillary sinusitis had a polyp of this kind Myers (1946) found only three choanal polyps in a material consisting of 25 000 otorhinolaryngological cases Heck Hallberg & Williams (1950) recorded 64 cases of choanal polyp (3 7 per cent) in a total of 1720 patients with nasal polyps Guthrie (1918) collected from the literature 116 cases of choanal polyp in young people under 16 years of age 14 of these were under 10 years A series of 30 000 cases of nasal polyp studied by Beco (1907) included only 4 child patients three of these with choanal polyp

It is generally considered that a choanal polyp is readily recognized by the otologist Often it is even visible on anterior rhinoscopy as a smooth grey blue mass in the posterior part of the nose At times in some cases the stalk of the polyp is seen in the middle meatus However the most important and surest diagnostic method is posterior rhinoscopy which reveals a formation blocking the choana partially or completely or even filling the whole of the nasopharynx Sometimes the polyp is seen extending downward beyond the soft palate Roentgen examination is often an aid towards diagnosis in most cases shadowing is present at least to some extent in the maxillary sinus on the side of the polyp (Heck Hallberg &

Williams, 1950, Hardy, 1957). A shadow referable to the polyp may appear in the lateral or axial roentgenogram It is usually not difficult to differentiate a choanal polyp from nasopharyngeal fibroma or some other tumour of this region

Treatment consists in removal, and most authorities have recommended severing of the pedicle with a hook, scissors, knife or snare (Lange, 1887, Killian, 1906, Guthrie, 1918, Stawraski, 1928; von Baykay, 1933, Thomson & Negus, 1947, Waldapfel, 1951, Hardy, 1957) Radical maxillary operation has been considered indicated if there is a recurrence or a chronic suppurative maxillary sinusitis, which latter is a rare occurrence (Hardy, 1957) Many others also claim that, to avoid recurrence of polyp, the mucosal area where the pedicle arises should be removed (von Baykay, 1933) Radiotherapy has been found of no avail (von Baykay, 1933)

There are very few data on recurrence of choanal polyps Heck, Hallberg & Williams (1950) reported a recurrence rate of 26 6 per cent Hardy states that with careful selection of cases and in experienced hands, a rate of 20 per cent may be reached

The Author's Own Investigations

During the period 1945–1958 a total of 118,374 patients were examined at the Otolaryngological Clinic of the University of Helsinki nasal polyps were discovered in 1295 Of these latter, 80 had choanal polyps The choanal polyps thus accounted for 0 07 per cent of all otorhinolaryngological cases and for 6 2 per cent of all cases of nasal polyp

The above 80 cases of choanal polyp have been studied with the object of throwing light on the following points (1) *age and sex distribution*, (2) roentgenological findings, (3) symptoms suggesting allergy, (4) simultaneous occurrence of other types of nasal polyps, (5) treatment, (6) histology, (7) tendency to recurrence

Inquiries were sent to the patients at the beginning of November 1960 asking them to present themselves for follow-up examination A total of 33 patients (41 per cent) came for follow-up Nineteen patients returned the questionnaires with their replies The case reports show that 8 additional patients had been re examined within two years or more of their first polypectomy done in our Clinic Thus there are at least some kind of follow-up data for 60 patients (75 per cent) observed for a period of 2 to 13 years

The *age and sex distribution* is given in Table 1

As seen in the table, there were 46 male and 34 female patients Only one of the women, aged 68, was over 40 years The men, however included 10 who were over 40, the oldest was 74 The majority of both the male and female patients were from 10 to 29 years old when presenting themselves for treatment There were 12 girls and 8 boys among the patients under 16 years of age The youngest patient was a boy of 6 years

Heck, Hallberg & Williams and Hardy have stated that a choanal polyp

TABLE 1 *80 cases of choanal polyp Age and sex classification*

Age (years)	Number of cases	Male	Female
Under 10	5	2	3
10 19	25	12	13
20-29	24	15	9
30 39	15	7	8
40 49	3	3	—
Over 50	8	7	1
	80	46	34

most frequently occurs in adults My own records show however, that the disease is as common in teenagers as in adults and seems to be comparatively rare in persons over 40 the age groups 10 to 39 years included 64 cases i e 80 per cent of the total the 10 to 25 year olds representing over one half

The sex ratio in my series was similar to that reported by Heck Hallberg & Williams whereas in Hardy s series there was a distinct female predominance

The choanal polyps were on the right side in 49 cases on the left in 30 and in one case polyps occurred bilaterally

Roentgen examination was made in 48 cases (60 per cent) of the total 80 None of these patients had an entirely normal roentgenogram Thirty two cases (68 per cent) showed a distinct shadow in the maxillary sinus on the side of the polyp frequently also in other sinuses of the same side In 15 cases (32 per cent) a shadow was present bilaterally in spite of the polyp being unilateral The shadow referable to the polyp was seen extending into the nasopharynx in 12 cases It appeared chiefly in the lateral view but often also in the axial view

Allergy plays a part in the etiology 34 patients (42 per cent) had a history of definite or possible allergic disease such as asthma hay fever eczema nasal polyposis Only two were definitely cases of asthma

Other coincidental nasal polyps were present in 6 out of the total 80 cases (7.5 per cent) at the time of the first removal of choanal polyp at the Otolaryngological Clinic Thus in the great majority of cases (92.5 per cent) the choanal polyp was the only nasal polyp present Polyps had been previously removed in the case of 26 patients but in only 2 cases was there a record of a choanal polyp having been removed

Removal of choanal polyp was generally performed for the first time by severing the pedicle with a hook More infrequently a snare or Weil s forceps was used Eight patients were treated by the Caldwell Luc approach when first admitted for treatment 2 by maxillary sinus trepanation and removal of polyps and of pedicle if present and one in whom the pedicle

seemed to arise from the posterior ethmoid cells, by evacuation of these cells. Four additional patients had a maxillary sinus operation when subsequently admitted for treatment. A total of 7 patients showed a distinct pedicle in connection with maxillary sinus operations. In the rest, the maxillary sinus mucosa was polypoid to the extent that no stalk could be discerned.

A biopsy was taken for *histological examination* in 18 cases of choanal polyp, the sections were stained with Weigert's iron hematoxylin and van Gieson solution. In all these cases the structure was that of an ordinary nasal polyp. These histological specimens did not differ distinctly from ordinary nasal polyps even in the presence of cell infiltration.

Recurrences. Follow-up data are available in 60 cases for a period of two years or more after the first removal of choanal polyp at our Clinic. Average observation time was 6.5 years.

In 20 of the above cases (33 per cent) a new polyp, probably choanal, developed. Of these patients, 10 were under 20 years of age, 7 were 20 to 29 years old, and the remaining three were 30 years or over.

Almost all the patients who had a return of choanal polyp had either evident or possible allergic disease on the basis of case records and follow-up data. 8 had asthma, allergic rhinitis or eczema, one had attacks of sneezing or a watery, swollen nasal mucosa "of allergic appearance".

Recurrence of choanal polyp was diagnosed in none of those 5 patients answering the questionnaire or seen at follow-up, who were subjected to maxillary sinus operation in connection with the first removal of choanal polyp. Maxillary operation was performed on 7 patients in connection with subsequent polypectomies. Thus a total of 12 of those 60 patients for whom follow-up data were available had a maxillary trepanation made with or without a Caldwell-Luc operation.

No regularity whatever was observed as regards recurrence of choanal polyps. The 20 patients in whom a polyp recurred included 5 with several recurrences. Polypectomy was necessary three to four times in these cases, in one patient as many as six times. The interval between removals varied from one year to ten years and could be even six years in the cases with several recurrences.

It was found that all 33 patients who were seen in follow-up did detect and identify the smell of acetic acid, ammonia and benzene with each nostril. The replies to the follow-up inquiries also showed that choanal polyps had no markedly impairing effect on the olfactory sense.

In the case of all patients who came for follow-up the condition of the nasal accessory sinuses was determined as far as possible by means of roentgen-ray examination or diaphanoscopy of the maxillary and frontal sinuses. If the result of diaphanoscopy seemed in the least doubtful a roentgenological examination was made or at least puncture and lavage of the maxillary sinus. The maxillary sinuses were examined by roentgen rays in a total of 20 patients of those seen in follow-up. Seven of these

showed an entirely normal result. All those five patients who showed a recurrence on follow-up examination had a definite roentgenological shadow at least on the side of the polyp. Generally the shadow seen roentgenologically in the sinuses could be interpreted as thickened, polypoid mucosa. The roentgenological or diaphanoscopic finding had become normal in definitely over half of the 33 follow-up examined patients who had had a choanal polyp; the finding on diaphanoscopy was entirely normal in 12 patients.

Mucus was obtained from only three sinuses when maxillary puncture and lavage were performed on the side of the polyp in those cases which showed the most marked shadowing. The fluid was fairly clear and yellowish in all cases. One of the patients revealed a recurrence of choanal polyp at follow-up examination, the other two were free of polyps.

CONCLUSIONS

The series consists of 80 cases of choanal polyp. Follow-up data were available regarding 60 cases. The follow-up period was at least two years, on an average 6.5 years.

Choanal polyp is a comparatively rare condition. It occurs most commonly in teenagers and young adults, and it is equally frequent in males and females.

In most cases a choanal polyp is traced to one maxillary sinus, which then almost invariably shows some degree of shadowing. However, suppurative maxillary sinusitis is a fairly rare phenomenon in these cases. Relatively rarely, in 7.5 per cent of the cases, were there other coincidental nasal polyps.

Extraction of the polyp leads to a good permanent result in about 60 per cent of the cases. Radical maxillary operation seems to be an almost sure method to avoid recurrences. However, it seems advisable not to resort to this radical method until recurrence has appeared following the simpler operation method above.

There is a particularly great tendency to recurrence in cases of choanal polyp associated with other nasal polyposis and in those in which a roentgenological shadow appears also in sinuses other than the maxillary sinus from which the choanal polyp arises.

The typical choanal polyp evidently is a pathological condition distinguishable from other nasal polyposis: it mostly occurs singly as the result of disease limited to one maxillary sinus and if removed in such a case recurs relatively seldom.

ZUSAMMENFASSUNG

Diese Untersuchung umfasst ein Material von 80 Choanalpolypfallen. In den Krankenberichten der Ohren-, Nasen- und Halsklinik der Universität Helsinki während der Periode 194[illegible]–1958 machten diese 80 Choanalpolypen nur 0.07%

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der Gesamtzahl der behandelten Fälle aus. Insgesamt wurden von 60 behandelten Patienten nachträgliche Berichte ermittelt. Die Beobachtungszeit war mindestens 2 Jahre und durchschnittlich 6.5 Jahre.

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VESTIBULAR SYMPTOMS PROVOKED BY HEAD AND NECK ROTATION AFTER BILATERAL CAROTID LIGATION

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In a 53-year-old woman ligation of both common carotid arteries resulted in vestibular symptoms provoked by neck torsion. These symptoms were not present before the operations. Electronystagmography before the ligations showed no nystagmus but neck torsion afterwards provoked nystagmus whereas positional tests without rotation of the neck gave no nystagmus. It is concluded that a vestibular test with electronystagmography before carotid or vertebral artery ligation might be used as a functional test on the circulation in the posterior communicating arteries in the circle of Willis. If neck torsion gives vestibular symptoms this circulation may not compensate adequately for vestibular ischaemia. The pre-operative vertebral angiogram and pre- and post-operative electronystagmography in the present case appear to support this hypothesis.

Vestibular symptoms following a disturbance of the blood flow in the vertebral arteries on rotation of the head and neck were described by DeKleyn & Nieuwenhuyse (1927) and DeKleyn (1939). Several authors have since dealt with this problem and the literature has been summarized by Sandström (1962) and Fields (1967). Ligation of both common carotid arteries in a patient with bilateral carotid-cavernous fistulas gave us the rare experimental situation in a human subject of complete dependence on the vertebral arteries for the cerebral blood flow and the opportunity of studying the pre- and post-operative oto-neurological conditions.

Case Report

A 53-year-old woman sustained a head injury in 1962. X-ray examination revealed a skull fracture. A few weeks after the trauma a pulse synchronous bruit in the head developed combined with diplopia, impaired vision, injection of the conjunctivae and increased intraocular pressure. In July 1963 carotid angiography showed bilateral carotid-cavernous fistulas and vertebral angiography showed filling of the anterior and medial cerebral arteries on both sides. Opera-

This investigation was supported by the Swedish Medical Research Council. Project 25X 36 01.

der Gesamtzahl der behandelten Fälle aus Insgesamt wurden von 60 behandelten Patienten nachträgliche Berichte ermittelt Die Beobachtungszeit war mindestens 2 Jahre und durchschnittlich 6,5 Jahre

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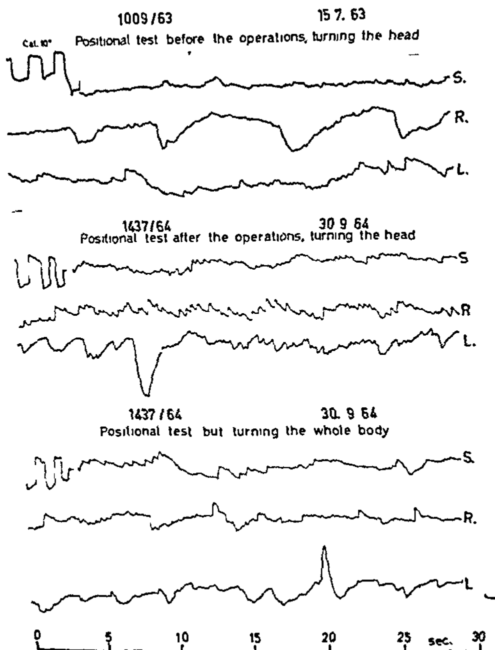
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[illegible] a nystagmus beating towards the same side as the rotational direction of the head. Note the difference between the two records marked *R* and *L* at the examination 30.9.64. In the supine position a *right* beating nystagmus was recorded, probably due to a central vestibular lesion encephalopathy.

tion 4.10.63: Ligation of the left common carotid. Operation 8.1.64: Ligation of the right common carotid. After the second operation the bruit disappeared completely and all visual symptoms subsided. A slight left-sided abducens palsy and moderate symptoms of post-traumatic encephalopathy remained.

After ligation of both carotid arteries the patient developed a new symptom, however. She complained of vertigo but only when rotating the head and neck to the sides, most pronounced to the right. She had definitely not had this symptom before the ligations. Oto-neurological examination before the operations had shown no spontaneous or positional nystagmus. Nystagmography was performed with the patient in the supine position and with the eyelids closed, and with rotation of the head alone into the lateral positions. The caloric responses were symmetrically normal. Pure tone audiography showed a 30 dB receptive hearing loss in the left ear and a 20 dB loss in the right, both more pronounced in the low frequencies. Oto-neurological examination after ligation *of both carotids gave different nystagmic findings. In the supine position a few* beats to the right were observed. Rotation of the head into the right lateral position resulted in an intense right beating nystagmus combined with a sensation of turning. Rotation of the head into the left lateral position changed the *direction of the nystagmus, a left-beating nystagmus was now recorded but* was less intense than the previous one which beat to the right. If, however, the patient's head was brought into the lateral positions by turning the body as a whole, thus eliminating torsion of the neck, no nystagmus was then recorded. These tests were repeated several times with the same results. Caloric testing in the supine position showed a slight directional preponderance to the right. As the patient showed a slight right-beating nystagmus when in the supine position this caloric asymmetry was regarded as insignificant.

No signs of cervical spondylosis.

DISCUSSION

Patients who have had bilateral ligation of the carotid arteries are unusual but not rare. Cases have been described by Penzholz (1954), Arnulf (1957) and Pardal (1959). The present case with vestibular symptoms developing after carotid ligations is, however, rather unusual in that objective nystagmic recordings could be made before and after the operations under such clinical conditions that they could be correlated both qualitatively and quantitatively.

It may be assumed that the patient had approximately the same blood flow in the vertebral artery before and after the operations and that the mechanical influence on the arteries by torsion of the head and neck was the same. Nevertheless, there was a marked difference in the vestibular findings. Before the ligation torsion of the neck did not result in any

Fig. 1. Electronystagmography before (15.7.63) and after (30.9.64) bilateral ligation of the carotid arteries. Calibration 10° horizontal eye movements. S = supine, *R* = right lateral and *L* = left lateral position of the head. Before the operations no significant nystagmus was recorded. After ligation of both carotids torsion of the head and neck

municating system in the circle of Willis must be considered. Sugar & Buey (1954) find here the explanation why some patients survive bilateral ligation of the vertebral artery. Fields (1963), in discussing the effect of vascular disorders on the vestibular system, also illustrates the importance of the circle of Willis by angiograms and post mortem examinations. The fact of whether or not compression of the vertebral arteries results in vestibular symptoms should consequently depend on a fourth factor, the function of the posterior communicating arteries in the circle of Willis.

With this argumentation in mind we consider that the present case may add something worth bearing in mind to the clinic. To find out whether the posterior communicating arteries allow a good blood flow a vestibular test may be performed just as in the case described. The absence of vestibular symptoms on head and neck torsion should indicate a good circulation in the circle of Willis and the presence of vestibular symptoms in cases where the carotid or vertebral arteries are not yet ligated must be regarded as a contraindication to ligation.

It is also worth stressing that on performing such vestibular tests objective nystagmic recordings should be made with the patient's eyelids closed, thus eliminating visual influences on the vestibular nystagmus. As pointed out by Aschan, Bergstedt & Stahle (1956), Jongkees, Maas & Philipszoon (1962) and Aschan (1963) the visual influence on vestibular nystagmus is rather large. If the precaution of eliminating visual influences is not taken a test such as that described will be rather misleading. Electronystagmography with closed eyelids must be the method of choice and the test should be performed with and without head torsion just as illustrated in the figure. A differential diagnosis between vestibular symptoms manifested by nystagmus due to central lesions (positional test with rotation of the body as a whole) can thus be made from intermittent (vascular) ischaemia (head and neck torsion). This is illustrated in the nystagmograms from 30.9.64 in the figure.

ZUSAMMENFASSUNG

Bei einer 53jährigen Frau entwickelten sich nach einer Kopfverletzung bilaterale karotid-kavernöse Fisteln. Nach Ligatur beider Kopfschlagadern verschwanden die meisten Symptome, aber es entwickelten sich Zeichen von vestibularer Funktionsstörung. Bei Rechts- oder Linksbewegung des Kopfes klagte die Patientin über Schwindel, der aber bei Rückbewegung des Kopfes in die Sagittalebene sofort verschwand. Ein Vergleich der Elektronystagmogramme vor und nach dem Eingriff zeigte, dass der postoperative Schwindel durch einen nach Halsdrehung gestörten Blutzufluss in der Arteria vertebralis erklärt werden konnte. Nystagmographie von karotider Ligatur kann die durch Angiographie gewonnenen Daten über den Blutzufluss in den Verbindungsschlagadern im Circulus Willisii ergänzen.

subjective or objective vestibular symptoms On the other hand the vertigo and nystagmus observed after ligation of the carotids must be attributed to a reduced vertebral blood flow following neck torsion. The most probable explanation is to be found in the pre-operative vertebral angiogram, which revealed an extremely good circulation in the circle of Willis If the biostatic behaviour of the vertebral arteries was the same on both occasions, the absence of vestibular symptoms before the carotid ligation must be explained by compensatory blood flow from the carotids After the operations such compensation was lacking and consequently a change in the vertebral blood flow resulted in an asymmetrical blood supply to the vestibular system, manifesting itself in vertigo and nystagmus Two observations in this patient support this hypothesis, disregarding the angiogram Firstly the change in position of the head could not be responsible for the post-operative vertigo and nystagmus because a change in position without neck torsion gave no symptoms Secondly the positive findings in the lateral positions were exactly opposite to one another, one side could be described as the image of the other

The beat direction of the nystagmus provoked by head and neck rotation was the same in this patient as in 7 out of 8 cases examined with the same technique by Sandström (1962) His explanation was that the torsion of the cervical spine in his patients with cervical deformities caused ischaemia in the vestibular system on the side opposite to the direction of rotation

In the discussion on vestibular symptoms resulting from rotation of the head and neck three main eliciting factors have been suggested

(1) Cervical spondylosis resulting in a mechanical obstruction of the vertebral artery by torsion of the cervical spine

(2) Anomaly of the vertebral arterial system allowing intermittent compression of the cervical course of the artery by the scalene muscles

(3) More or less pronounced "normal" compression of the vertebral artery as a normal biostatic phenomenon

The first two factors should both result in vestibular symptoms, especially when combined with the third factor These phenomena have been discussed from different aspects by Powers, Drislane & Nevins (1961), Sandström (1962) and Fields (1963) For further interpretation of this case, however, the basic observation made by DeKleyn & Nieuwenhuyse (1927) and DeKleyn (1939) and later supported by Tissington-Tatlow & Bammer (1957) and Toole & Tucker (1960) is essential, namely that a rotation to one side usually results in compression of the vertebral artery on the opposite side The vestibular symptoms would thus be elicited by ischaemia in the vestibular system on *the side opposite to the rotational direction* As, however, the incidence of vestibular symptoms on head rotation is much smaller than that of, for example, deformities in the cervical spine, other compensatory factors must be taken into account Here the com-

HAIRS OF THE COCHLEAR SENSORY CELLS AND THEIR ATTACHMENT TO THE TECTORIAL MEMBRANE

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The hairs of the sensory cells in the cochleae were studied with emphasis on their attachment to the tectorial membrane. So far we have observed that the peripheral row of tall hairs of the W form and a few inner rows at its base were shallowly but firmly embedded in the tectorial membrane. The hair tops were more electron dense and delimited from the tectorial membrane by the unit membrane of the sensory cell. The hairs of the inner sensory cells were likewise arranged in a W form with the tallest hairs in the peripheral row. Modified cilia and numerous short hairs or microvilli were demonstrated at the base of the W in the sensory cells of the undifferentiated organ of Corti but were lacking in the specimens of older animals.

INTRODUCTION

The sensory hairs of the cochlea have been of great interest to investigators since their general morphology was presented by Held (1926) and Kolmer (1927). It was generally considered that bending of the hairs was essential for excitation of the sensory cells in the organ of Corti (Davis 1959). Engström, Ades & Hawkins (1962) believed that the hairs act as levers transmitting mechanical energy from the tectorial membrane to the basal body, the essential excitable structure of the sensory cell. Vinnikov & Titova (1964), as a result of their histochemical investigations, considered the hair surface a synaptic membrane. There have been numerous morphological studies made on the sensory hairs of the cochlea including those by Engström & Wersäll (1958), Smith & Dempsey (1957), Spoendlin (1959, 1960), Iurato (1961) and Kimura, Schuknecht & Sando (1964). However these studies did not provide detailed information on the structural relationship between the hairs and the tectorial membrane. Although two types of sensory hairs in the cochlea were described by Held (1926) and Kolmer (1927), up to the present time only the stereocilia have been observed. In the present investigation we have studied the hairs from various species with special emphasis on hair attachment to the

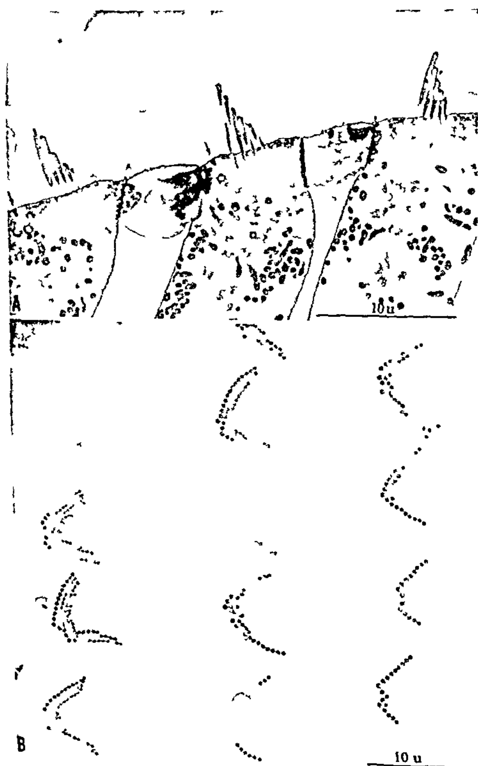
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MATERIALS AND METHOD

Cochleae of the human, rhesus monkey, squirrel monkey, cat, guinea pig, bat and mouse were studied The method of preparing specimens for electron microscopy is described elsewhere (Kimura & Wersäll, 1962, Kimura *et al*, 1964) The specimens were fixed with 1% buffered osmium tetroxide (Millonig, 1961), intravitally in the bat and cat, within five minutes after death in the mouse and guinea pig, and within three hours in the human In monkeys under Nembutal anesthesia, the fixative was introduced directly into the cistern of the vestibule after stapedectomy and round window puncture The other ear was fixed in a similar manner but within a few minutes after death The cochlea, after partial removal of the otic capsule in all turns, was dehydrated and embedded in Epon (Luft, 1961) The dissected specimens were cut with an LKB ultrotome, stained with alcoholic uranyl acetate and lead hydroxide (Karnovsky, 1961) and examined with the Siemens Elmskop 1 with magnifications ranging from ×1000 to ×40,000

FINDINGS

When the hairs of each outer sensory cell were examined in cross section, they were arranged in a W form (Fig 1 B), the base of which faced the Hensen's cells The number of parallel rows of hairs forming the W varied in different species about five to seven rows in the human, five to six in rhesus and squirrel monkeys, and three rows each in the cat, guinea pig, mouse and bat (Fig 2) In the human the W pattern was occasionally asymmetric some hairs of one limb of the W and peripheral hairs, including those at the base of the W, were missing Sometimes at the base of the W a giant hair was seen in place of several hairs The hairs in the peripheral rows of the W were taller than those of the inner rows (Fig 1) In the outermost sensory cells or third row, the hairs at the base of the W form were longer than those in a similar position in the outer sensory cells located closer to the modiolus The hairs of the apical turn were taller than those of the basal turn, but the number of hairs of each sensory cell was fewer For example, in the squirrel monkey, measurements

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Fig 1 *A* Electron micrograph showing three outer sensory cells with their tall hairs touching the tectorial membrane Note the obliquity of hair insertion in the sensory cells on the left Arrows show position of basal bodies Squirrel monkey *B* Cross section of hairs of three rows of outer sensory cells the base of the W form faces the Hensen's cells Note the large hair at the base of the W in one sensory cell Basal turn rhesus monkey



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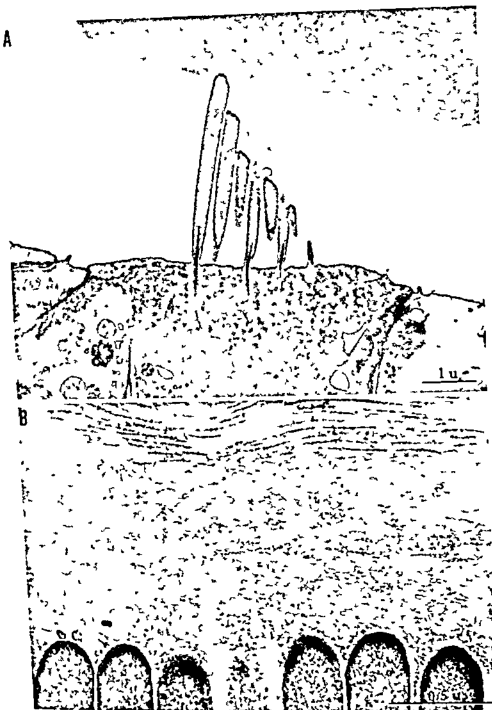


Fig. 3. Hair attachment (outermost sensory cell, squirrel monkey) to the tectorial membrane. *A*. An example typical of hair attachment seen in the present series. *B*. Longitudinal section of hairs in the peripheral row of the W form. Note the narrow spaces between the hairs, small circular membranous structures near the dark hair tops and coarse filaments above the granular layer of the tectorial membrane.

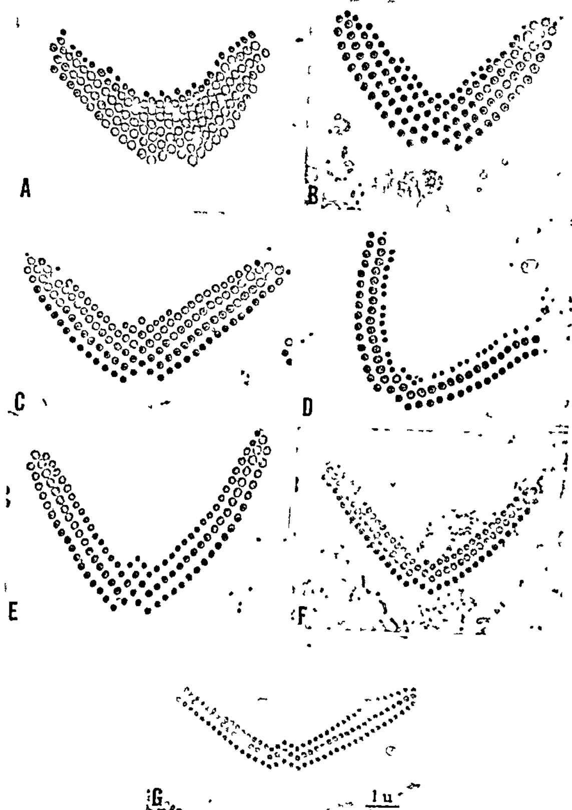


Fig. 2 Electron micrographs of W's composed of hairs cut in cross section near the reticular lamina of a basal turn outer sensory cell of different species. All photographs were taken and printed at the same session with magnification remaining constant. Figures denote numbers of hairs counted. *A* Human (142). *B* Rhesus monkey (121). Note a basal body at the base of the W. *C* Squirrel monkey (134). *D* Cat (97). *E* Guinea pig (116). *F* Mouse (102). *G* Bat *Myotis lucifugus* (124).

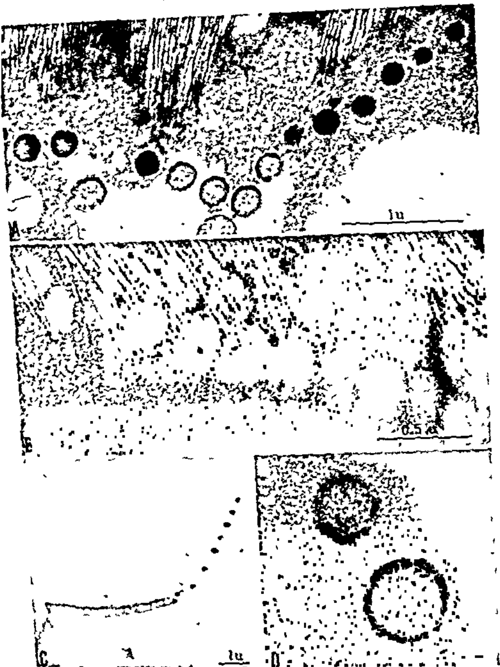


Fig. 5. Cross section of hair tops in the tectorial membrane. *A*: Dark hair tops of peripheral row and base of the W form. Squirrel monkey. *B*: Single peripheral row of the W in the tectorial membrane after hairs were pulled away. Squirrel monkey. *C*: Peripheral row of W with some hairs intact in the tectorial membrane. Bat, *Myotis lucifugus*. *D*: High magnification of cross section of hair tops in the tectorial membrane. Squirrel monkey.

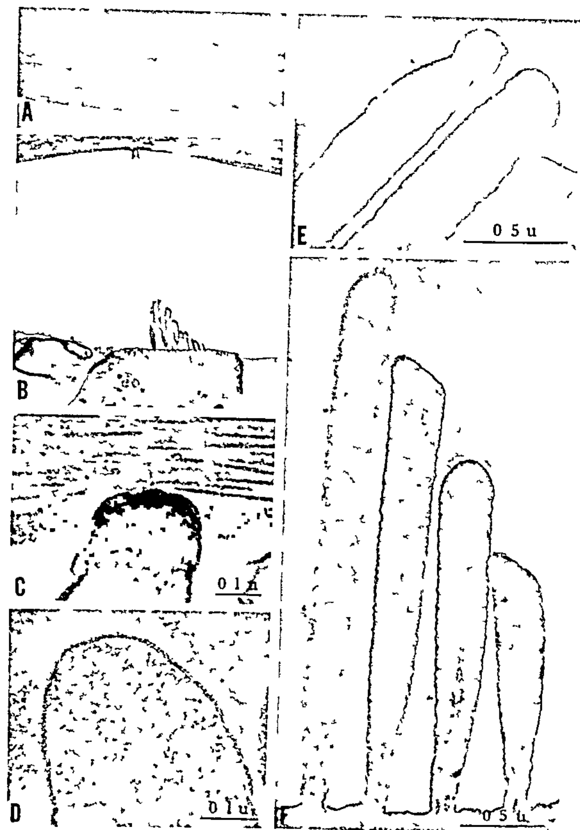


Fig 4 A Two notches remaining after tall hairs of two sensory cells were pulled away from the tectorial membrane radial section Guinea pig *B* Lifted tectorial membrane with a broken tall hair *C* Broken hair of second row outer sensory cell in contact with coarse filaments *D* Hair tip with unit membrane in the granular layer of the tectorial membrane *E* Swelling of a hair tip within the tectorial membrane and the granular layer between hairs *F* Longitudinal section showing granular material around hair tops Squirrel monkey *B F*

Fig. Hairs of the outer sen r cells A The cut cular plate w th W formed b a l la al l od Second turn B Ba al bod and ce tr ole n the cut cle ne f ly *outer* sensory cell Guinea p g C An open la e root bridged b electr n nse ma lal Note the l ght z ne arrow per pheral to the ha r c re abo e the u n a plae D A long tale root with clu ers f small granules extend ng int pla m *F* A la e *root* ex e d ng cl e t the ntracel ular peripheral membrane F The ha r oo and w r e l ke structure Squ rrel m nke A C D E F

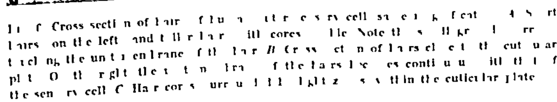
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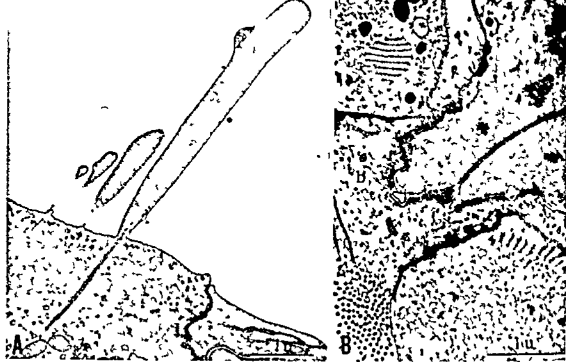
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I i f Cross secti n of hair f lu a t t r e s ry cell su e i g f cat 4 S rt hairs on the left and t ll r h r ill cores He Note th s ll gr l rr hairs on the left and t ll r l a r ill cores t i el ng the un t i enl rane f th h i r *B* Cr ss ct n of h rs el e t th cut u ar pl t O th r gl t the t t n lra f the hairs l e es conti u u ill th l f the sen ry cell *C* Ha r cor s urr u l l l l gl t z s t th in the cuticular plate



Fig. 9 Electron micrographs demonstrating cilia in both inner and outer sensory cells of the one-day-old mouse cochlea. A, Cilium (arrow) and centriole located near the tall hairs in the top outer sensory cell. N, nerve ending. B, Cilium and centriole in an inner sensory cell. IS, ... OS, outer sensory cell. C, Cilia (arrows) of both inner (IS) and outer sensory cells oriented in the same direction. D, Cross section of hairs of the outer sensory cells showing cilia at the base of the W's. Note the numerous rows of hairs and microvilli. Compare with the W form of hairs in ten-day-old mouse shown in Fig. 21. The insert shows higher magnification of a cilium without two central [illegible]



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Fig. 8 Apical zone of the inner sensory cell. *A* Longitudinal section of hairs of different lengths. Note the bleb near the hair top and extension of the hair root into the cytoplasm. Squirrel monkey. *B* Cross section of the cuticular plate of the inner sensory cells demonstrating striated structures. (P) pillar cell top. (b) border cell. Normal cat. *C* Cross section near the hair tops of four inner sensory cells. Note the notches at the bases of the W forms (arrows) and proximity of the hairs of these sensory cells. Guinea pig. *D* The W pattern in three inner sensory cells. Rhesus monkey. *E* The W form with a notch at its base (arrow) near which a basal body is seen. Guinea pig.



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were made on hairs attached to the tectorial membrane and the heights averaged as follows: apical turn: outermost row, 5.7 μ, middle row, 5.1 μ, inner row, 4.9 μ; second turn: outermost row, 5.2 μ, middle row, 4.9 μ, inner row, 4.6 μ; basal turn: outermost row, 2.2 μ, middle row, 1.6 μ, inner row, 1.7 μ. The number of hairs in one basal turn sensory cell was about 135, 120 in the second turn, and 80 in the third. However all these measurements varied somewhat among cells in the same cochlear turn. It was noted that the sensory cells proper were taller at the higher turns and they also became gradually taller in the radially outermost row.

The hairs of the outer sensory cell in side view resembled a baseball bat, being broad along most of its length and narrowing abruptly near the cuticular plate (Figs. 3 A, 4 F). The diameter of a tall hair of the basal turn in the squirrel monkey was about 3000 Å near its insertion into the tectorial membrane and about 1500 Å at its origin near the cuticular plate. The distance between hairs attached to the tectorial membrane in the peripheral row of the W, measured near the hair tops, was about 180 Å to 500 Å (Fig. 3 B).

At the lower margin of the tectorial membrane where the hairs were attached, granular material was concentrated, frequently forming a dense layer in which fine filamentous structures were sometimes apparent (Figs. 3 B, 4 C, 5). The larger, radially oriented filaments of the tectorial membrane were visible above the hair tops, but a few times, in the inner row sensory cells, they appeared to be directly on the tops of the hairs (Fig. 4 C). From the lower surface of the tectorial membrane short processes extended toward the hairs.

The tops of only the tall hairs were embedded in the tectorial membrane (Figs. 1, 3, 4, 5); at the base of the W, hairs of one to three rows appeared to attach (Fig. 4 F) but at the outer limb of the W form only the peripheral row hairs were seen in the tectorial membrane (Fig. 5). The tops of the the attached hairs were surrounded by the unit membrane of the sensory cell (Fig. 4 D); their penetration was shallow, about 0.1 μ to 0.4 μ in the squirrel monkey. Immediately outside and adjacent to the unit membrane of the hairs was a slight light zone which was traversed by thread-like material of the tectorial membrane (Fig. 5 A); however, this light zone might represent a preparation artifact. Just above the hair tops there were often small circular structures with an inner light area surrounded by a unit membrane. The matrix of the hair top appeared very dark, its density varying somewhat in different hairs (Figs. 3 B, 4 C, 5).

Fig. 10. Electron micrographs showing the relationship between the tectorial membrane, sensory and supporting cells of the basal turn in a ten day old mouse. *A*. The tectorial membrane touches the reticular lamina and Hensen's cell. Note a slight demarkation between the edge and main body of the tectorial membrane. *B*. The tectorial membrane is loosely attached to the supporting cells. *C*. The attachment zone of the tectorial membrane is filled with numerous coarse granules, which are also present in unstained sections.

hairs resembling microvilli, located at the inner angle of the W (Fig 9 D), but they were not apparent, nor were the modified cilia, in specimens of the ten day old mouse (Fig 2 F)

In the organ of Corti of the ten day-old mouse, the top of the tectorial membrane was found attached to the outer zone of the reticular laminar and less frequently to the Hensen's cells (Figs 10 A, 10 B), but in other corresponding areas of the same specimen, there was only granular precipitate which was not attributable to the staining methods (Fig 10 C) In specimens of the adult, this region remained clear and the attachment was not observed

DISCUSSION

It was previously indicated by Kolmer (1927) and Kimura, Schuknecht & Sando (1964) that hairs of the peripheral rows of the W were taller than those of the inner rows In the present investigation we have demonstrated that the tall hairs at the periphery, and a few rows at the base of the W (squirrel monkey) are attached to the tectorial membrane (Figs 3, 4, 5) The question of whether the short hairs are free below the tectorial membrane or attached to processes of it is not completely decided by this study The granular substance similar to that of the tectorial membrane which is seen between the short hairs suggests that the short hairs may touch the tectorial membrane *in vivo* Mechanical vibrations of tall hairs could be transmitted to other hairs of different heights, since the sensory hairs approximate each other near their tops, and much granular material is present between the hairs (Figs 3 B, 4 E, 4 F)

The present study shows that hair tops in the tectorial membrane are surrounded by a unit membrane (Fig 4 D) continuous with that of the sensory cell proper We support the descriptions given by Iurato (1961) and Engstrom *et al* (1962) that the sensory hairs and filaments of the tectorial membrane are not structurally continuous, this is in contrast to the view held by Mygind (1948) and Borghesan (1952, 1957) in their light microscopic investigations

Although the hair tops are embedded shallowly in the tectorial membrane they are held firmly, hairs are found bent in the direction of shrinkage of the tectorial membrane or even torn, their top portions remaining intact in the tectorial membrane (Figs 4 B 4 C) The strong attachment of the tectorial membrane to the organ of Corti was previously reported in fresh and live cochleae by Hilding (1952), Békésy (1953) and Tonndorf, Duvall & Reneau (1962) In the young mouse the depth of hair penetration does not vary greatly regardless of whether or not the tip of the tectorial membrane is attached to the reticular lamina and Hensen's cells (Fig 10)

Flock (1964), investigating the lateral line organ of fish reported that there was a concentration of electron dense material in the gelatinous

At the narrow neck of the hair just above the cuticular plate the granular material of the hair matrix was aggregated toward a central core thus leaving a light region between the unit membrane and the core (Figs 3A 4I 6 7C) The hair core at the level of the cuticular plate appeared solid and tubular (Figs 6 7A 7B 7C) In the monkey and human there were often large granules in the hair matrix close to the unit membrane and central core (Figs 3A 4F 6A) Between the tall hairs was a thin layer of granular substance which was continuous with that of the tectorial membrane (Fig 4E) The fine granular substance was also seen between the hair surfaces of both long and short hairs but it was not continuous with the tectorial membrane

In the squirrel monkey the hairs of the basal turn were anchored to the sensory cell at an angle of about 30 degrees in respect to the long axis of the outer sensory cells (Fig 1A) which in turn were tilted in the opposite direction in respect to the basilar membrane Many hair rootlets particularly of the short hairs terminated in the cuticular plate the rootlets of the tall hairs from the primate cochleae extended some distance into the cytoplasm sometimes accompanied by clusters of fine granules (Fig 7D) A few long hair rootlets were seen very close to and perhaps even touching the intracellular peripheral membrane (Fig 7I) From the lower margin of the cuticular plate long filaments or layer like structures about 1000 Å apart were found extending deep into the cytoplasm (Fig 7F) they were not connected to the hair proper and often ran parallel to the hair rootlets or sometimes horizontally below the cuticular plate The region between these structures contained a homogeneous substance similar to that of the cuticular plate and occasionally a fine granular layer

Inner sensory cell hairs were large in diameter about 3200 Å at the top and 1900 Å at the neck (Fig 8A) and as tall or even taller than those of the outer sensory cells The hair tops were not seen attached to the tectorial membrane nor were there sharp outlines of the hair tops or torn hair tops in the tectorial membrane The hairs were also arranged in a W form with a notch at its base which faced the Hensen s cells (Figs 8C 8D 8E) The hair tops were close together and as a result distinction between sensory cells at this level was difficult Hairs of the peripheral row and of one other row at the base of the W near the pillar cells were taller than others (Figs 8A 8C) In the cuticular plate and apical cytoplasm there were striated structures with alternate dark and light streaks The dark streaks were about 1300 Å apart (Fig 8B)

Cilia were observed in the sensory cells of the cochlea of the one day old mouse (Fig 9) they were located at the base of the W of both the inner and outer sensory cell hairs (Figs 9B 9C) Nine pairs of peripheral filaments in the cilia were distinct while the two central filaments were inconspicuous or absent (Fig 9D) Similar cilia were also found in the Deiter s cells and in the internal sulcus cells There were numerous short

hairs, resembling microvilli, located at the inner angle of the W (Fig 9 D), but they were not apparent, nor were the modified cilia, in specimens of the ten day old mouse (Fig 2 F)

In the organ of Corti of the ten day old mouse, the top of the tectorial membrane was found attached to the outer zone of the reticular laminar and less frequently to the Hensen's cells (Figs 10 A, 10 B), but in other corresponding areas of the same specimen, there was only granular precipitate which was not attributable to the staining methods (Fig 10 C) In specimens of the adult, this region remained clear and the attachment was not observed

DISCUSSION

It was previously indicated by Kolmer (1927) and Kimura, Schuknecht & Sando (1964) that hairs of the peripheral rows of the W were taller than those of the inner rows In the present investigation we have demonstrated that the tall hairs at the periphery, and a few rows at the base of the W (squirrel monkey) are attached to the tectorial membrane (Figs 3, 4, 5) The question of whether the short hairs are free below the tectorial membrane or attached to processes of it is not completely decided by this study The granular substance similar to that of the tectorial membrane which is seen between the short hairs suggests that the short hairs may touch the tectorial membrane *in vivo* Mechanical vibrations of tall hairs could be transmitted to other hairs of different heights, since the sensory hairs approximate each other near their tops, and much granular material is present between the hairs (Figs 3 B, 4 E, 4 F)

The present study shows that hair tops in the tectorial membrane are surrounded by a unit membrane (Fig 4 D) continuous with that of the sensory cell proper We support the descriptions given by Iurato (1961) and Engström *et al* (1962) that the sensory hairs and filaments of the tectorial membrane are not structurally continuous, this is in contrast to the view held by Mygind (1948) and Borghesan (1952, 1957) in their light microscopic investigations

Although the hair tops are embedded shallowly in the tectorial membrane, they are held firmly, hairs are found bent in the direction of shrinkage of the tectorial membrane or even torn, their top portions remaining intact in the tectorial membrane (Figs 4 B, 4 C) The strong attachment of the tectorial membrane to the organ of Corti was previously reported in fresh and live cochleae by Hilding (1952), Bekesy (1953) and Tonndorf, Duvall & Reneau (1962) In the young mouse the depth of hair penetration does not vary greatly regardless of whether or not the tip of the tectorial membrane is attached to the reticular lamina and Hensen's cells (Fig 10)

Flock (1964), investigating the lateral line organ of fish, reported that there was a concentration of electron dense material in the gelatinous

At the narrow neck of the hair just above the cuticular plate, the granular material of the hair matrix was aggregated toward a central core, thus leaving a light region between the unit membrane and the core (Figs 3 A, 4 F, 6, 7 C). The hair core at the level of the cuticular plate appeared solid and tubular (Figs 6, 7 A, 7 B, 7 C) In the monkey and human, there were often large granules in the hair matrix close to the unit membrane and central core (Figs 3 A, 4 F, 6 A) Between the tall hairs was a thin layer of granular substance which was continuous with that of the tectorial membrane (Fig 4 E). The fine granular substance was also seen between the hair surfaces of both long and short hairs, but it was not continuous with the tectorial membrane

In the squirrel monkey, the hairs of the basal turn were anchored to the sensory cell at an angle of about 30 degrees in respect to the long axis of the outer sensory cells (Fig 1 A) which in turn were tilted in the opposite direction in respect to the basilar membrane Many hair rootlets, particularly of the short hairs, terminated in the cuticular plate, the rootlets of the tall hairs from the primate cochleae extended some distance into the cytoplasm, sometimes accompanied by clusters of fine granules (Fig 7 D) A few long hair rootlets were seen very close to, and perhaps even touching, the intracellular peripheral membrane (Fig 7 E) From the lower margin of the cuticular plate long filaments or layer-like structures, about 1000 Å apart, were found extending deep into the cytoplasm (Fig 7 F), they were not connected to the hair proper and often ran parallel to the hair rootlets or sometimes horizontally below the cuticular plate The region between these structures contained a homogeneous substance similar to that of the cuticular plate, and occasionally a fine granular layer

Inner sensory cell hairs were large in diameter, about 3200 Å at the top and 1900 Å at the neck (Fig 8 A), and as tall or even taller than those of the outer sensory cells The hair tops were not seen attached to the tectorial membrane, nor were there sharp outlines of the hair tops or torn hair tops in the tectorial membrane The hairs were also arranged in a W form with a notch at its base which faced the Hensen's cells (Figs 8 C, 8 D, 8 E) The hair tops were close together and, as a result, distinction between sensory cells at this level was difficult Hairs of the peripheral row and of one other row at the base of the W, near the pillar cells were taller than others (Figs 8 A, 8 C) In the cuticular plate and apical cytoplasm there were striated structures with alternate dark and light streaks The dark streaks were about 1500 Å apart (Fig 8 B)

Cilia were observed in the sensory cells of the cochlea of the one-day-old mouse (Fig 9), they were located at the base of the W of both the inner and outer sensory cell hairs (Figs 9 B, 9 C) Nine pairs of peripheral filaments in the cilia were distinct while the two central filaments were inconspicuous or absent (Fig 9 D) Similar cilia were also found in the Deiter's cells and in the internal sulcus cells There were numerous short

plate of the inner sensory cell (Fig 8 B) appear structurally similar to those seen in a comparable area of the vestibular sensory cells (Friedmann et al 1963 Iceland & Farkashidy, 1963 Hilding & House, 1964) These striated structures are seen in both normal and abnormal sensory cells, but their functional significance is presently unknown

ACKNOWLEDGMENTS

The valuable technical assistance of Miss Victoria Diez Canseco and Miss Maureen O Donnell is gratefully acknowledged

ZUSAMMENFASSUNG

Der Verfasser untersuchte die Haare der akustischen Sinneszellen und widmete besondere Aufmerksamkeit ihrer Beziehung zur Membrana tectoria Die Reihe der peripheren hohen Haare, die einen W förmigen Saum bilden, sowie einige innere Reihen von Haaren waren an der Basis flach aber fest in die Membrana tectoria eingebettet Die Spitzenpartie der Haare war elektronenoptisch dunkler und wurde durch eine Grenzmembran der Sinneszelle von der Membrana tectoria getrennt Die Haare der inneren Sinneszellen bilden ebenfalls eine W-förmige Reihe wobei die höchsten Haare peripher stehen Im Entwicklungs-*stadium* wurden Cilien an der Basis des W angetroffen jedoch fehlten diese im entwickelten Cortischen Organ

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substance around the kinocilia, and that the tops of the stereocilia contained a dark granular substance. Vinnikov & Titova (1964) reported acetylcholinesterase activity in the hairs of the organ of Corti, and postulated that the hair surface, acting as a synaptic membrane, was depolarized by acetylcholine in the moving endolymph. We have seen electron dense material accumulated at the hair tops of tall and short hairs (Figs. 1 B, 3 B, 5 A, 5 D), although we have *not yet employed histochemical methods* to determine its nature.

There has not yet been evidence presented that the hairs of the inner sensory cell are attached to the tectorial membrane, and Engström *et al.* (1962) doubted that this was the case. So far we have not seen any attachment, or torn hair top, in the tectorial membrane. If the inner sensory cell hairs do attach, their relationship to the tectorial membrane probably would not be as strong as that of the outer sensory cells. The inner sensory cells are located just above the relatively rigid tympanic lip of the limbus spiralis, while the outer sensory cells are found over the basilar membrane, in a position to receive much mechanical vibration, therefore, the outer sensory hairs may require a stronger attachment to the tectorial membrane. In acoustic trauma it is well known that the outer sensory cells are affected more severely than the inner sensory cells, it is also possible that the hairs may be detached from the tectorial membrane, or be otherwise damaged.

De Vries (1949), freezing the cochlea with liquid nitrogen, and Hilding (1952) and Tonndorf *et al.* (1962), using intravital staining methods, believed that the tip of the tectorial membrane was attached to the Hensen's cells in adult specimens. Our present study failed to demonstrate this connection in adult specimens, although its attachment to the outer edge of the reticular lamina is definitely observed in developmental phases of the organ of Corti.

Held (1926) and Kolmer (1927) described cilia in the cochlear sensory cells, but we are reasonably certain that they are not present (Figs. 1 A, 7 B) or are very rare in normal adult specimens. However, we have demonstrated modified cilia at the base of the W in the undifferentiated inner and outer sensory cells of the one-day-old mouse (Fig. 9). Wersäll (1965) also observed them in the cochlear sensory cells of the human fetus. The cilia in *our specimens lacked the two central filaments, as did those described* in the retinal rod by De Robertis (1956), Tokuyasu and Yamada (1959) and by Fawcett (1961). These cilia differ from the kinocilia in the vestibular sensory cells in that the latter have two central filaments as well as nine peripheral ones. Flock, Kimura, Lundquist & Wersäll (1962) and Engström *et al.* (1962) demonstrated basal bodies in the adult outer sensory cells, in a position *comparable to that occupied by the modified cilia in the* present study.

The filamentous or striated structures seen with the hair roots below the cuticular plate of the outer sensory cell (Fig. 7 F) and in the cuticular

MECHOLYL AND NORADRENALIN TESTS FOR VERTIGO

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The Mecholyl test and noradrenalin test were administered on 21 patients suffering from vertiginous diseases in order to clarify its relation to the functional activities of the central autonomic nervous system The patients with vertigo showed a common tendency to the hypofunction of the sympathetic center and the hyperfunction of the parasympathetic center in the hypothalamus Both the Mecholyl curve and the noradrenalin curve in almost all the patients with vertigo showed each particular type, to which the authors gave the name of "vertigo type". The Mecholyl test results were improved by means of adequate treatment, whereas no significant change was found in the noradrenalin test results

Though it is well known that some kinds of vertigo are closely connected with the autonomic nerves, little has been written on the relation between the functional test results of the autonomic nerves and vertigo The authors have tried to apply the Mecholyl test and noradrenalin test on patients suffering from vertiginous diseases in order to clarify the functional activities of their central autonomic nervous system

METHODS

1 *Mecholyl test*

After the blood pressure and the pulse-rate of the subject became stable, 10 mg of metacholine hydrochloride (Mecholyl) per 60 kg of body weight was injected intramuscularly Then the arterial blood pressure was measured for 25 minutes, twice a minute for the first 5 minutes and thereafter once a minute for the remaining 20 minutes At the same time the side effect of Mecholyl was observed The values measured were composed as a graph showing a curve (Mecholyl curve) on the scale of 1 cm to a minute in the abscissa and of 1 cm to 5 mm Hg of the systolic pressure in the ordinate. The zero-point in the ordinate indicated the systolic pressure before the injection of Mecholyl The data were represented numerically by means of Abe's method (Abe *et al*, 1960 and 1963) as shown in Fig 1 In the figure, C represents the area which is surrounded by the ascending part of the blood pressure curve and the line that starts from the lowest point of the blood pressure which is parallel with the basal line,

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TABLE 1

O D Orthostatic disorder M D Ménière's disease M S Menière's syndrome

Group	Subject	Age Sex	Disease	Mecholyl test Abe's index	Noradrenalin test PI
Non cured group	1	19, F	O D	0.59	0.35
	2	22 F	O D	1.90	0.43
	3	39, F	O D	1.60	0.44
	4	54, F	O D	1.87	0.89
	5	34, F	M D	1.95	0.59
	6	44 F	M D	1.83	0.32
	7	49 M	M D	2.15	0.50
	8	31 F	M S	1.71	0.79
	9	35 F	M S	1.82	0.67
	10	40 M	M S	1.91	0.01
	11	53, M	M S	1.88	0.47
Cured group	12	18 M	O D	2.02	1.00
	13	41, F	O D	2.26	0.10
	14	42, F	O D	2.59	1.90
	15	26, F	M D	2.39	0.16
	16	38 F	M D	2.28	0.27
	17	41, M	M D	2.09	0.60
	18	50 M	M D	2.50	0.42
	19	40, F	M S	2.61	1.92
	20	41, M	M S	2.20	0.94
	21	48 F	M S	2.74	1.09
Normal group	22	18, M		3.41	2.85
	23	22 F		3.21	4.20
	24	26, F		3.30	3.21
	25	28, M		3.23	2.50
	26	30 M		3.27	3.86

10 cured Five normal subjects without vertigo and vestibular dysfunction were also tested for the sake of contrast observation

The results obtained are shown in Table 1 According to Abe's method (Abe *et al* 1960 and 1963) the patients with vertigo showed statistically significant lower values than the normal subjects Among the patients with vertigo the non-cured group showed lower values than the cured group In the former group, a value of more than 2.0 was attained by only one patient whose posttreatment value, however, was significantly larger than that of pretreatment, approaching the normal value

The noradrenalin test revealed that the PI value was significantly smaller in the group with vertigo than in the normal group No significant difference was found between the cured and the non-cured group

Figs 2 to 4 are typical examples of the Mecholyl and noradrenalin curves The Mecholyl curve of the patient with vertigo, regardless of its origin, was characterized by its small rising gradient It showed a markedly slow

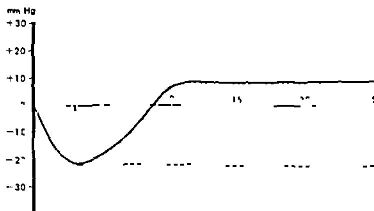


Fig. 1. Mecholyl test (Abe's method). C/h = Abe's Index.

while h is the maximum variation of the pressure. The ratio C to h is called "Abe's Index". Subjects who show a ratio of more than 3.76, a ratio of between 2.09 and 3.76, and one less than 2.09 are labelled as "Sympathetic hyperreactor", "Normoreactor" and "Sympathetic hyporeactor" respectively.

2. *Noradrenalin test* (Nelson & Gellhorn, 1957; Kanai, 1963)

After the blood pressure and the pulse-rate of the subject became stable, 0.05 mg of noradrenalin was given intravenously for a minute. This method required measurement of the arterial blood pressure and the pulse-rate (pulse-rate per minute was computed as six times the pulse beat for 10 seconds) of the subject. The measurements were taken twice a minute for the first 5 minutes, once a minute for the next 5 minutes and every other minute for the remaining 10 minutes. The change in the blood pressure which covered the whole period of the observation was represented as a curve (noradrenalin curve). Among the total processes, the highest value of the arterial pressure and the minimum number of the pulse-rate were picked up and then the Parasympathetic Index (PI) was reckoned by means of the following formula.

$$PI = \frac{\text{The highest value of the arterial pressure } (a) - \text{The arterial pressure before noradrenalin injection } (b) / b}{\text{The pulse rate before noradrenalin injection } (c) - \text{The minimum pulse rate in the whole process } (d) / c}$$

This value may range generally in 0~6. The PI value is considered to be inversely proportional to the reactivity of the parasympathetic center in the hypothalamus.

RESULTS

21 patients with vertigo were chosen at random for the experiments, 7 suffering from orthostatic disorder, 7 from Ménière's disease, and 7 from Ménière's syndrome. They were divided into 2 groups, 11 non-cured and

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O D Orthostatic disorder M D Ménière's disease M S Ménière's syndrome

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Figs 2 to 4 are typical examples of the Mecholyl and noradrenalin curves. The Mecholyl curve of the patient with vertigo, regardless of its origin, was characterized by its small rising gradient. It showed a markedly slow

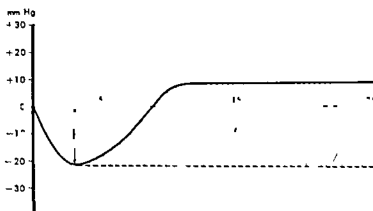


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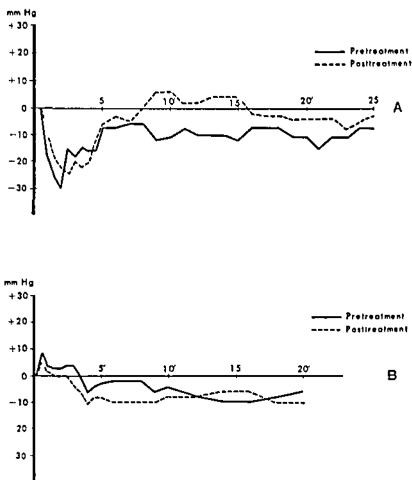


Fig. 2. Mecholyl curve (A) and noradrenalin curve (B) of case 1.

recovery to the basal line, that is, the arterial blood pressure before the Mecholyl injection. The noradrenalin curve of the patient with vertigo was characterized by a low peak in the rising part of the curve followed by *its sinking part underneath the basal line. It did not return to the basal* line or it continued descending for 20 minutes after the noradrenalin injection.

As these forms of the Mecholyl and noradrenalin curves were found to be common to almost all the patients with vertigo, the authors designated them "vertigo type".

From these results obtained in the present study, the conclusion can be drawn that the patients with vertigo have a tendency toward the hypofunction of the sympathetic center and the hyperfunction of the parasympathetic center in the hypothalamus.

DISCUSSION

The Mecholyl test, which was applied in this study to test the function of the central autonomic nervous system, has been used to estimate the prognosis of electric shock in psychiatry. The significance of the Mecholyl

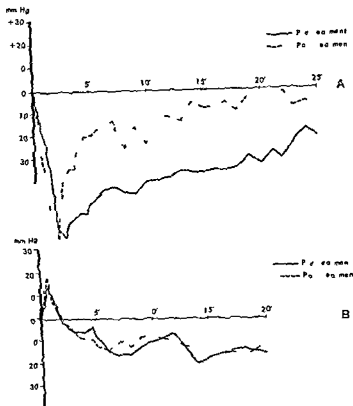


Fig. 3. Mecholyl curve (*A*) and noradrenalin curve (*B*) of case 16

test was disclosed in Gellhorn's experimental study (Gellhorn & Redgate 1955, Gellhorn 1956, Gellhorn, Nakao & Redgate 1956). He found that *the first time* Mecholyl is injected to the subject it decreases the blood pressure through the contraction of the peripheral blood vessels by its cholinergic action. Then the sympathetic center in the posterior part of the *hypothalamus* is excited by the impulses from the carotid sinus and the *blood* pressure is increased. The recovering curve of the blood pressure

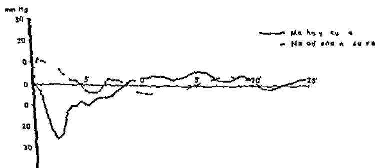


Fig. 4. Mecholyl curve and noradrenalin curve of case 23

after the Mecholyl injection shows the activity of the sympathetic center localised in the posterior part of the hypothalamus.

Tasaka *et al.* (1959) and Okinaka *et al.* (1959) confirmed the test-retest reliability of the Mecholyl test. Abe *et al.* (1960) observed the close relationship between the values of the Mecholyl test and the clinical findings in the patients with dysfunction of the autonomic nerves.

On the other hand, the noradrenalin test is not yet widely used. In 1948 Funkenstein used adrenalin in his Adrenalin-Mecholyl Test (Funkenstein *et al.* 1948), but because of its side effect, Nelson came to use noradrenalin instead of adrenalin (Nelson & Gellhorn 1957).

When noradrenalin is injected, at first it increases the blood pressure and causes bradycardia. These changes excite the parasympathetic center in the anterior part of the hypothalamus. Thus, the noradrenalin test is regarded as indicating the function of the parasympathetic center.

An obviously significant difference in PI values in the noradrenalin test was found between normal subjects and patients with vertigo, the latter showing lower PI. Contrary to the Mecholyl test results, no significant difference was discovered in the PI values between the cured group and the non-cured group. This fact may suggest an underlying predisposition to vertigo.

It should be noted that regardless of the kind of vertiginous disease, the phenomenon "vertigo" had a direct connection with the above-mentioned tendency of the Mecholyl and noradrenalin curves. In other words, this tendency seemed to imply that the phenomenon "vertigo" is related to a uniform abnormality of the autonomic nervous system independent of the cause of the symptom.

ACKNOWLEDGMENT

The authors wish to express their gratitude to their director, Prof. Dr. T. Suzuki, for many valuable suggestions.

ZUSAMMENFASSUNG

Der Mecholyl- und der Noradrenalin-Test wurde bei einundzwanzig unter Schwindel leidenden Patienten angewendet, um die Beziehung zu den funktionellen Aktivitäten des zentralen autonomen Nervensystems abzuklären. Die unter Schwindel leidenden Patienten zeigten alle eine Neigung zu einer Hypofunktion des sympathischen Zentrums und zu einer Hyperfunktion des parasympathischen Zentrums im Hypothalamus. Sowohl die Mecholyl- als auch die Noradrenalinkurve zeigten bei nahezu allen unter Schwindel leidenden Patienten denselben typischen Verlauf, dem die Autoren den Namen „vertigo type" gaben. Die Ergebnisse des Mecholyl-Tests konnten mittels entsprechender Behandlung verbessert werden, während keine signifikante Veränderung in den Ergebnissen des Noradrenalin-Tests festgestellt wurde.

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CONCOMITANT VISUAL STIMULATION DOES NOT ALTER HABITUATION OF NYSTAGMIC, OCULOGYRAL OR PSYCHOPHYSICAL RESPONSES TO ANGULAR ACCELERATION

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This experiment evaluated the influence of various types of visual stimulation upon the habituation of nystagmic, oculogyral, and psychophysical responses to angular acceleration. Four groups of 20 young men each were given a series of 16 angular accelerations of 24°/sec² magnitude and of 10 sec duration. Concomitant visual stimulation, varied between groups from total darkness to full room illumination, was introduced on habituation trials that were interpolated between test trials. Although highly significant decrements for all responses were found with repeated testing, the different visual conditions in no way altered this habituation.

Repeated angular acceleration leads to a progressive diminution of certain vestibular responses. Man undergoes a systematic reduction of ocular nystagmus (Dodge, 1923), his subjective velocity declines (Guedry, Collins & Sheffey, 1961), and the duration of the oculogyral illusion decreases (Griffith, 1920). The reader may refer to three recent reviews of the vestibular habituation literature (Crampton, 1964, Wendt, 1964, Guedry, 1965).

It has been well established by many studies that an animal's nystagmic response habituates even to moderate acceleration values and with visual stimuli excluded (e.g., Mowrer, 1934). This habituation is prominent in cat when severe alerting measures prevent drowsiness from attenuating the response (Crampton & Schwam, 1961). The data for man have not been as clear. Certainly a reduction in nystagmic activity has been shown in members of special occupations, dancing and skating (Mowrer, 1934), and piloting high performance aircraft (Aschan, 1954). But, until recently the only systematic laboratory data showing habituation of the human nystagmic response during testing with vision excluded was that of Dodge (1923), who employed only himself, and offered data in which a loss of alertness could account for the nystagmic decrement (Collins, Crampton & Posner, 1961). The interpretation by Wendt (1951) that loss of alertness accounted for the loss of nystagmic activity and the extensive data by Hauty (1953) and Collins (1962) in which alertness was controlled and in which habituation did not occur, indicated that perhaps man did not

habituate to moderate acceleration intensities when vision was excluded These findings led to the conclusion that the prominent habituation found among members of these special occupations is probably due to the high intensity of the accelerations and/or the concomitant visual stimulation (Crampton 1962 *a*) Then subsequent data by Collins (1964) showed man did habituate to moderate levels of acceleration and in total darkness Since a considerable part of the total slow phase decrement occurs over the first few accelerations (Collins 1964 Brown 1965) it is likely that habituation was not observed earlier by Hauty and Collins because the practice or preliminary trials were not considered and most of the habituation took place in these preliminary accelerations The question of whether vision is a significant variable for nystagmic habituation in man remains and is the primary object of this experiment

The importance of visual stimulation for habituation of the oculogyral effect (OGI) is a matter of little agreement Griffith (1920) found the effect to habituate markedly (decrease in duration) with full room illumination Graybiel & Hupp (1946) however found no habituation for either full room illumination or the more usual small target light condition Similarly no habituation for the oculogyral effect was found by Clark & MacCorquodale (1949) or Brown Imus Niven & Graybiel (1949) But later and from the same laboratory reports described habituation of the response and related the habituation to varieties of visual experience permitted during and following angular acceleration (Brown & Guedry 1951 Guedry 1950 1952) This experiment re examines this question

There is no definitive study of the habituation of subjective estimates of angular velocity A subject does indicate a progressive decline in apparent velocity with successive testing but the experiment that bears on this point was not directed toward an evaluation of the influence of visual stimulation on habituation (Guedry Collins & Sheffey 1961) The visual stimulus has not been varied systematically between groups to provide a direct and unequivocal evaluation

Examination of these studies reveals differences in experimental design nature of the visual material when and how such material was introduced species selected for subjects and control of angular acceleration and arousal The purpose of this experiment is to evaluate the influence of vision upon the habituation of nystagmic oculogyral and psychophysical responses to angular acceleration

For this purpose an acceleration of 24°/sec and 10 sec duration was selected In addition to using a relatively high level acceleration and examining the three responses to angular acceleration the following features were incorporated into the experimental design (*a*) since previous work with high level accelerations has indicated that nystagmus may continue for 3 4 min following the termination of the acceleration a minimum of 5 min was allowed between all trials (*b*) the level of arousal was carefully controlled by requiring the subject to estimate his subjective velocity (*c*) all

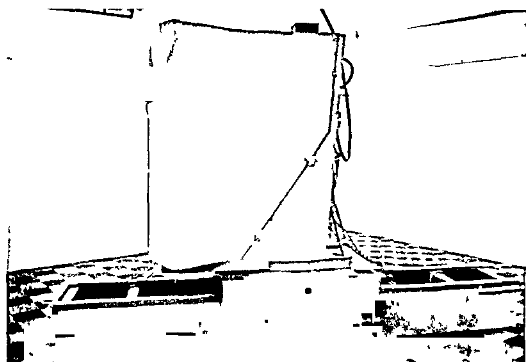


FIG 1 Angular accelerator with removable capsule enclosing the subject

subjects were normal young men and "naive" with regard to experimental acceleration experience, (*d*) the visual environment was systematically *varied between experimental groups rather than as a more complex within-groups variable*, (*e*) precise control over angular acceleration was provided, (*f*) second-by-second nystagmic slow-phase measurement was accomplished rather than measuring only the less reliable durations

METHODS

Stimulator

The angular accelerator consisted of a hydraulically driven rotating beam that supported the subject's chair (Brown & Crampton, 1964) A removable capsule entirely enclosed the subject, permitting control of visual stimulation and eliminating cues of rotation associated with air movement across the body (Fig 1) A ventilating fan and a small "dither" motor provided low-level masking vibration and noise to further reduce cues of actual machinery rotation Electronic voice communication between subject and operator was provided The chair was positioned so that the subject's head was over the rotatory axis and an adjustable bite board maintained the subject's head in a fixed position

Recording

Electrodes were taped near the outer canthi of the eyes, and an indifferent electrode placed in the center of the forehead Eye movements, the

periods of acceleration and signals which the subject initiated by pressing a key were transmitted via slip rings to an Offner Type T ink writing recorder situated in an adjacent control room. Eye movement potentials were amplified with a 1.4 sec RC time constant and displayed with a 25 mm/sec paper speed.

Calibration

Prior to each subject's first acceleration and again following his last, a 10° voluntary displacement of the eyes was used to obtain a calibration relating mm of recorded slow phase movement with actual angular rotation of the eyes (Brown & Crampton 1964).

Procedure

Each subject was instructed to keep his eyes open and directed straight ahead throughout the experimental session of 16 trials. Each trial consisted of a 24°/sec² acceleration maintained for 10 sec, with 5 min constant velocity between trials. The first trial was always a positive acceleration from 0–40 RPM, the next a negative acceleration from 40–0 RPM. This alternation was continued throughout the 16 trials. The first and last two trials were the same for all 80 subjects. Specifically, on trials 1 and 15 all subjects were instructed to fixate a single dim light and report the cessation of the horizontal movement of the light (the oculogyral illusion). On trials 2 and 16, testing was conducted in total darkness and all subjects were instructed to indicate the cessation of their sensation of primary subjective velocity. For all of these common trials, subjects reported the appropriate cessation by depressing a signal key twice in rapid succession. In addition, the subjects were required to make subjective estimates of their velocity during and following an acceleration by pressing the signal key every time they felt they had passed through a 90° arc. Both nystagmus and subjective responses were recorded on all of the common trials, but nystagmus was scored only for trials 2 and 16.

On trials 3 through 14, the habituating trials, the subjects again were instructed to indicate subjective velocity as well as the cessation of the sensation of rotation. On these trials the visual environment was different for each group of 20 subjects. Group I was given the habituating series in total darkness. Group II was habituated with a single dim fixation light. Group III was habituated with the interior of the capsule lighted, and Group IV received the habituation series with the room lights on and the capsule canopy removed. Although subjects assigned to Group IV could visually monitor their velocity during the habituating trials, they also were required to estimate their velocity on all trials.

A general outline of the experimental design is provided on Table 1. The visual conditions permit the assessment of the role of the visual environment in the habituation of nystagmic, psychophysical and oculogyral

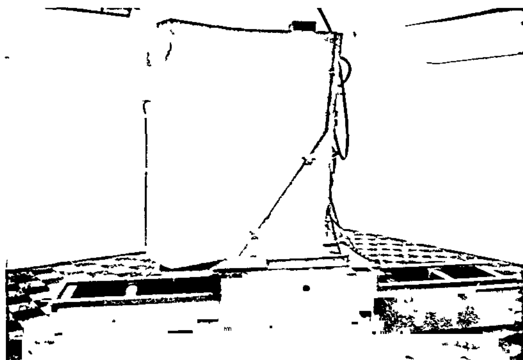


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A general outline of the experimental design is provided on Table 1. The visual conditions permit the assessment of the role of the visual environment in the habituation of nystagmic, psychophysical, and oculogyral

TABLE 1 *Experimental design*

Groups	Trials 1	2	3–11	15	16
I	OGI	Darkness	Darkness	OGI	Darkness
II	OGI	Darkness	OGI	OGI	Darkness
III	OGI	Darkness	Capsule lights	OGI	Darkness
IV	OGI	Darkness	Room lights	OGI	Darkness

responses to angular acceleration. (*a*) nystagmic habituation can be evaluated across visual conditions by comparing slow-phase output on trials 2 and 16, the darkness trials, (*b*) oculogyral habituation can be evaluated in the same manner by comparing oculogyral duration responses on trials 1 and 15, (*c*) habituation of the psychophysical response can also be evaluated by comparing the durations of the subjective estimates of velocity on trials 2 and 16

RESULTS

The variability and dispersion of responses to angular acceleration has led to the conclusion that geometric means are a more appropriate measure of central tendency for such data than arithmetic means (Brown & Crampton, 1964) Accordingly, geometric means were computed for all responses (nystagmus, oculogyral, and psychophysical) on each appropriate trial, the logarithmic data serving as the units for the analyses of variance and covariance This dual analysis, employed for each of the three responses, allows three questions The analysis of variance evaluates the effect of trials (T) on the groups, the differences between groups (G), and whether the trials influenced the groups differentially (the interaction G × T) The analysis of covariance for the same data takes into account the differences between groups on the pre-habituation measures in the evaluation of the differences between the groups on the post-habituation measures Of particular interest here is the interaction (G × T) and the analysis of covariance

Nystagmus

Nystagmic responses from all four groups for trials 2 and 16 as well as Group I data for trials 4, 6, 8, 10 12, and 14, were reduced by hand measurement The vertical magnitude of the slow-phase sweep of each primary nystagmic beat was measured in mm for each 1 sec segment of the record, summed across seconds for each trial, and then converted to degrees of slow phase eye movement according to the calibration obtained at the end of each experimental session An example of a typical nystagmus

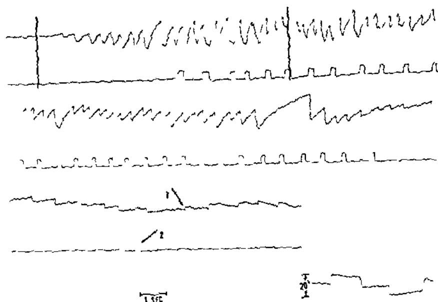


FIG 2 This sample, recorded at 25 mm sec, illustrates a typical nystagmus response to an angular acceleration of 2½° sec² (upper trace) Also shown are the key press responses the subject made to indicate his subjective velocity (lower trace) The vertical bars define the 10 sec period of acceleration and arrows 1 and 2 denote the onset of secondary nystagmus and cessation of the sensation of primary movement, respectively The close relationship between the subjective and nystagmic durations indicated in this record is not typical these responses typically show great variability in their relationship to each other

record and the associated subjective estimates of velocity is shown in Fig 2 The results of the statistical analyses are shown in Table 2 These data, along with appropriate nystagmus trials for the darkness group (Group I), are plotted in Fig 3 Both the analysis and inspection of the data clearly indicate that a highly significant reduction in nystagmic output occurs over trials However, the different visual environments do not systematically influence this habituation, and no differences exist between groups when the starting level is taken into account

Oculogyral Responses

The log durations of the oculogyral responses (trials 1 and 15) for all four groups also were treated by both analysis of variance and covariance These analyses are included in Table 2 and the data are plotted in Fig 4 Again it is quite evident that while significant habituation occurs from trial 1 to trial 15, the different visual conditions exert no effect upon this habituation.

TABLE 2 *Analyses of variance and covariance*

	Analysis of variance				Analysis of covariance			
	Source	*df*	*MS*	*F*	Source	*df*	*MS*	*F*
A *Nystagmic responses* (trials 2 and 16)								
Bet	Groups (G)	3	1078	4 90[a]	Groups	3	0245	2 2
	Ss w grps	76	0220		Error	75	0111	
With	Trials (T)	1	3580	43 66[a]				
	G × T	3	0061	—				
	T × Ss w grps	76	0082					
B *Oculogyral responses* (trials 1 and 15)								
Bet	Groups (G)	3	0423	—	Groups	3	0971	2 0
	Ss w grps	76	1036		Error	75	0481	
With	Trials (T)	1	5 4878	47 80[a]				
	G × T	3	0157	—				
	T × Ss w grps	76	1148					
C *Psychophysical responses* (trials 2 and 16)								
Bet	Groups (G)	3	0083	—	Groups	3	0374	1 6
	Ss w grps	76	0430		Error	75	0235	
With	Trials (T)	1	1 4160	50 57[a]				
	G × T	3	0518	1 85				
	T × Ss w grps	76	0280					

[a] Sig at 0 01 level

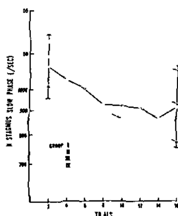


FIG 3 Average nystagmus slow phase output per trial for the 4 visual conditions The standard error of the mean for Group I is indicated on trials 2 and 16 to show the relative variability of the response

Psychophysical Responses

The log duration of the subjective estimates of velocity were obtained for all subjects on trials 2 and 16 and also treated by analysis of variance and covariance These analyses also are shown in Table 2 and the data are plotted in Fig 5 As with the nystagmic and oculogyral responses there

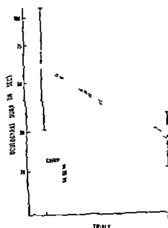


Fig 4 Average oculogyral duration on trials 1 and 15 for the 4 visual conditions

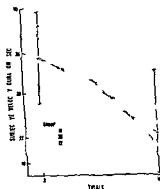


Fig 5 Average duration of subjective velocity estimates on trials 2 and 16 for the 4 visual conditions

is a significant response decline and vision neither hastens nor retards this habituation

Correlations

In addition to the three sets of responses already discussed (nystagmic slow phase oculogyral duration and subjective duration) the durations of each primary nystagmic response on trial 16 were compiled treated

TABLE 3 *Matrix of Pearson product moment correlation coefficients*

	Ny SI	Ny D	OGI	Psych
Nystagmus (slow phase)	—			
Nystagmus (duration)	+ 61	—		
Oculogyral (duration)	+ 04	10	—	
Psychophysical (duration)	+ 10	02	50	—

logarithmically, and compared with the other responses on trials 15 and 16 by means of Pearson Product-Moment correlations. The resulting intercorrelation matrix is shown in Table 3. The highest correlation was found between the two nystagmus measures (0.64). The only other relationship of any magnitude was found between oculogyral and psychophysical response duration (0.50). Of particular note are the small correlations between nystagmic and oculogyral measures (0.04 and 0.10)

DISCUSSION

The present data unequivocally substantiate previous findings that highly significant decrements for nystagmic, oculogyral, and psychophysical responses to angular acceleration result from repeated testing in man. The high level of alertness maintained throughout each trial minimized a response decline occasioned by a loss of alertness (Collins, 1962, 1964).

The results of the present study illustrate the importance of recording and scoring a subject's first exposure to the stimulus when nystagmic habituation is to be evaluated. Extensive nystagmic habituation most frequently occurs early in testing and failure to evaluate nystagmus on the initial exposure to acceleration can conceal the extent of the response decline. For example, in the present study the function describing nystagmic output in darkness (Fig. 3) is negatively accelerated with a slight but continuing decline on later trials. However, by far the greatest part of the total response decrement is evident during the first few trials. The importance of this "initial habituation" is further emphasized by noting that the retention of nystagmic habituation is largely restricted to only this initial part of the total response decline (Brown, 1965).

Although all three responses to angular acceleration demonstrated highly significant decrements with repeated testing, the different visual conditions in no way altered this habituation. These findings support Crampton's conclusion (1962 *b*) from work with the cat that vision does not influence nystagmic habituation.

Other and diverse findings relative to this question could result from several possibilities. One potential source of deviant findings is reflected in the variability of individual subjects. If a covariance design and geometric means are not used, an initial chance clustering of high- or low-responders within a single group can lead to spuriously significant differences between groups. There also is the possibility that vision exerts an influence on the habituation of responses to angular acceleration, but only under very special conditions.

The intercorrelations of the various dependent variables in Table 3 are an interesting addition to the basic data. As one would expect, the two nystagmus measures (duration and slow phase) correlate quite highly as do the two subjective measures (oculogyral and psychophysical). The extremely low correlations between the subjective and nystagmus measures

further accentuate the tenuousness of any close relationship between vestibular nystagmus and the oculogyral effect (Byford, 1963, van Dishoeck, Spoor & Nijhoff, 1954).

There were some incidents of nausea and vomiting. In no instance did this occur in Groups I or II, but 4 of the 20 *subjects in Group* III and 5 out of 20 in Group IV were replaced after disruption of the experimental session by disabling nausea and vomiting. Inasmuch as Groups III and IV received prominent concomitant visual stimulation, there is the clear implication of an unusual visual-vestibular interaction (Crampton & Young, 1953, Steele, 1963). Examination of the nystagmic records of the replaced subjects revealed no obvious differences when compared with the rest of the subject population.

The implication of the present study for the general situation in which one finds concomitant visual and angular acceleration stimulation is clearly that the presence or absence of visual stimulation is not of major significance to habituation.

ACKNOWLEDGMENT

The technical assistance of Randolph Cheatham and Larry Fish is gratefully acknowledged.

RÉSUMÉ

Cette expérience évalua l'influence de plusieurs types de la stimulation visuelle sur l'habituation des responses nystagmique oculo-gératoire et psychophysique à l'accélération angulaire. On donnait une série de 16 accélérations angulaires de 24° sec² d'intensité et d'une durée de 10 sec aux quatre groupes chacun de 20 *jeunes hommes*. Concomitante stimulation visuelle variée entre les groupes de l'*obscurité totale jusqu'à* une chambre pleinement éclairée était présentée sur les expériences l'habituation lesquelles étaient interpolées entre des *expériences* d'essai. Bien que des décroissements très importants fussent trouvés pour toutes les *réponses* avec de essais répétés les différentes conditions visuelles ne changaient pas cette *habituation*.

ZUSAMMENFASSUNG

Dieser Versuch wertete den *Einfluss verschiedener* Arten von optischen Reizen auf die Gewöhnung der nystagmischen oculogyrischen und psychophysikalischen Reakti*onen zu Kreisbeschleunigungen* aus. Vier Gruppen von je 20 jungen Männern wurden einer Reihe von 16 Kreisbeschleunigungen von 24° sec² und einer Dauer von 10 Sekunden *ausgesetzt*. *Begleitende* optische Reize, die bei den Gruppen von völliger Dunkelheit bis zu voller Raumbeleuchtung wechselten, wurden durch Gewöhnungsversuche eingeführt, welch letztere zwischen den eigentlichen Versuchen abgehalten wurden. Obwohl höchst bedeutsame Verminderungen bei allen Reaktionen nach *wiederholten* Versuchen gefunden wurden, änderten die verschiedenen optischen Bedingungen diese Gewöhnung in keiner Weise.

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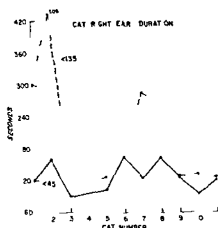


Fig 2 a

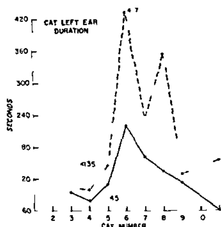


Fig 2 b

Fig 2 (a b) The duration of post-caloric nystagmus at angles of 135 and 45 (fronto-occipital axes) following bilateral irrigations in 11 cats Duration was greater at angle 135 than angle 45 in cats 1 2 8 and 10 (right ear) and cats 5 6 7 9 and 11 left ear

In the second group of 11 cats the experiment was repeated with different water temperatures (12 14 19 24 27 49°C) The findings of this group were quite similar to those of the first group Differences in duration of nystagmus for angles of 135° and 45° were greater when a stronger stimulus (12 and 14°C) was applied (Tables 1 a b)

Mean group values for 22 cats are presented in Table 2 When the cat s fronto occipital axis was placed at an angle of 135° mean duration of post caloric nystagmus for all cats was 68 sec longer than at an angle of 45

In examining the data from the different animals the question arises of

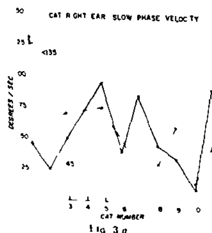


Fig 3 a

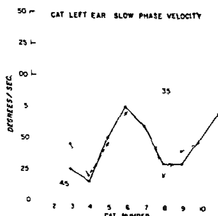


Fig 3 b

Fig 3 (a b) Maximum slow phase velocity at two different angles

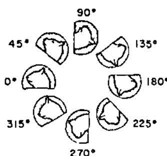


Fig 1 Different positions of the cat's head for vestibular testing Fronto-occipital axis at an angle of 45° is optimal position for caloric testing

the horizontal prone position until the fronto-occipital axis reached an angle of 45° (Fig 1) The fronto-occipital axis coincides with the position of the horizontal semicircular canal (Rademaker, 1926) In this position caloric stimulation was performed Water temperature used for irrigation ranged from 10°C to 49°C, and the duration of each irrigation was 40 sec After an interval of 10 min the cat's head was raised until the fronto-occipital axis reached an angle of 135° In this position the center of gravity was changed and the otoliths provoked maximal stimulation of the otolith sensorineural epithelium by traction The caloric test was then repeated with the same water temperature and the same length of irrigation provoking nystagmus in the same direction The order of angles (45° to 135°) was randomized in all cats

A four-channel recorder (Offner Type R) was used for nystagmus registration (Hinchcliffe & Voots, 1962) Channel 1 recorded the velocity of fast and slow eye movement (time constant 0 03 sec), Channel 2 registered the derivated curve of the slow phase Conventional nystagmus was recorded through the third channel (time constant 1 0 sec) and by Tektronix oscilloscope and Polaroid camera Channel 4 registered average frequency Paper speed was 1 mm/sec Duration, maximum slow phase and maximum fast phase velocity of post-caloric nystagmus were recorded and analyzed

RESULTS

In the first group of 11 cats the water temperature used for irrigation was 16°C It was found that nystagmus duration was longer when the fronto-occipital axis of the cat's head was placed in a 135° angle (right ear, cats 1, 2, 7, 8, 10) than at a 45° (Fig 2 *a*) There was less difference between the 45° and 135° angles in cats 3, 4 and 5 (20–40 sec) Two cats (9, 11) did not indicate any difference In the left ear the difference in nystagmus duration between 45° and 135° angles was even more obvious in cats 5, 6, 7, 9 and 11 (Fig 2 *b*)

Maximum slow phase velocity (Figs 3 *a* *b*) and maximum fast phase velocity (Figs 4 *a*, *b*) failed to demonstrate a consistent change in nystagmus reaction upon caloric testing at the 135° angle

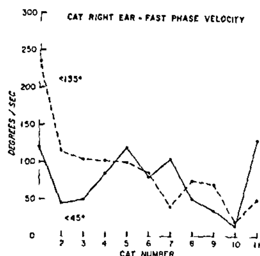
TABLE 1 b

Cat no	Temp	Ear	Angle	Duration (sec)	Maximum velocity Slow phase (deg/sec)	Maximum velocity Fast phase (deg/sec)
17	27°C	R	45	126	70	115
			135	135	70	105
		L	45	104	75	115
			135	120	50	70
18	27°C	R	45			
			135			
		L	45	97	70	160
			135	115	75	150
19	27°C	R	45	120	125	150
			135	125	100	125
		L	45	128	70	90
			135	186	100	155
20	27°C	R	45	134	25	45
			135	169	65	100
		L	45	127	40	70
			135	145	45	85
21	49 C	R	45	80	35	70
			135	100	40	70
		L	45			
			135	108	5	2
22	49°C	R	45	89	20	35
			135	159	50	70
		L	45	83	15	35
			135	134	35	60

whether the observed differences between the measures in the two positions are real or may simply be the result of the random variations one may expect in any set of measures. To test the hypothesis that there is no real difference between the measures in the two positions, the analysis of variance technic was used. The deviation measures from all animals were combined for this test of the position effect. Similar analyses were made

TABLE 2. *Mean values for duration of post caloric nystagmus in 22 cats with fronto-occipital axis at angles 45° and 135°*

		Angle	Duration (sec)
Mean value 22 cats	Right ear	45	119.15
		135	187.10
	Left ear	45	111.52
		135	179.52



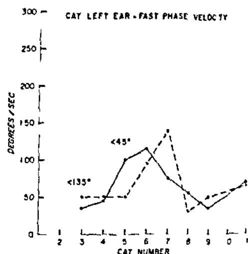


Fig. 4 (a, b) Maximum fast phase velocity at two different angles

TABLE 1 a. *Values for duration and maximum fast and slow phase velocities of post caloric nystagmus using various water temperatures with fronto occipital axis at angles 45° and 135°*

Cat no	Temp	Ear	Angle	Duration (sec)	Maximum velocity: Slow phase (deg./sec)	Maximum velocity: Fast phase (deg./sec)
12	12 C	R	45	[illegible]	70	100
			135	277	50	100
		L	45	137	35	60
			135	223	50	75
13	14°C	R	45	92	35	45
			135	115	20	20
		L	45	86	20	55
			135	112	20	30
14	19 C	R	45	168	80	120
			135	169	65	105
		L	45	156	95	125
			135	259	60	65
15	24 C	R	45	128	80	80
			135	228	70	70
		L	45	117	70	75
			135	137	75	75
16	24 C	R	45	91	55	100
			135	146	80	80
		L	45	114	70	70
			135	[illegible]	[illegible]	85

of mental alertness at the fronto occipital axis 135° angle could affect duration of nystagmus more than other parameters

RÉSUMÉ

Une epreuve calorique vestibulaire (10–49°C, duree de 40 secs) fut faite chez 22 chats places dans une position optimum pour la stimulation des canaux semicirculaires horizontaux (axe fronto-occipital à un angle de 45°) et dans une position ou les otolithes provoquent une stimulation maximum des cellules ciliares maculaires (axe fronto occipital a un angle de 135°) La sequence des angles utilisés fut choisie au hasard et les stimulations furent separes par des intervals de 10 min Le nystagmus fut enregistré électriquement avec un appareil a quatre canaux La durée du nystagmus post calorique et la vitesse des phases lente et rapide furent mesurees L epreuve calorique faite a un angle de 135° (angle maximum de stimulation pour l organe otolithique mais non optimum pour les canaux semicirculaires horizontaux) provoqua un nystagmus post calorique d une durée définitivement plus longue qu'a un angle de 45° Ainsi, le système otolithique peut agir comme un agent de control sur la duree du nystag mus post calorique ou la stimulation de l organe otolithique peut par elle meme produire le nystagmus dans certaines conditions physiologiques

ZUSAMMENFASSUNG

Es wurden vestibulär kalorische Reizungen (10–49°C, Dauer 40 sec) an 22 *Katzen durchgeführt* Die Versuchstiere befanden sich in optimaler Position für *die Reizung* des horizontalen Bogenganges (fronto okzipitale Achse in einem Winkel von 45°) und in einer Haltung in der die Otolithen die makularen Haarzellen *maximal* stimulieren (fronto-okzipitale Achse 135°) Die Reihenfolge der angewendeten Positionen bzw Winkel war dem Zufall überlassen die *Reizungen* waren durch Ruhepausen von 10 min zeitlich *getrennt Nystagmus* wurde elektrisch *registriert* mittels eines 4 kanaligen Geräts die Dauer des post *kalorischen* Nystagmus und Geschwindigkeit der Augenbewegungen in der schnellen und langsamen Phase wurden analysiert Die kalorische Untersuchung führte zu einer signifikant längeren *Dauer des postkalorischen* Nystagmus wenn sie im Winkel *von 135°* durchgeführt wurde (Maximalreiz für Otolithen aber kein *Optimalposition* für horizontalen Bogengang) gegenüber der Haltung im Winkel *von 45° Es lässt* sich daher *annehmen* dass das Otolithensystem als ein kontrollierender Mechanismus *für* die Dauer des postkalorischen Nystagmus wirken kann oder dass die Reizung des Otolithenorgans selbst imstande ist unter *physiologischen Bedingungen* Nystagmus zu produzieren

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of the combined data for the slow-phase velocity measures and for the fast-phase velocity measures. Of the three sets of data, only the duration measures yield a significant variance ratio ($F = 30.5$ where an F value of 8.02 or larger would be significant at the 1% level). This says in effect, that, for these particular sets of data, there is a statistically significant difference between the duration measures in the two positions but not for the velocity measures.

DISCUSSION

The relationship between the otolith system and nystagmus has been discussed by many authors. Borries (1923) stated that post-caloric nystagmus was the result of the cooling or warming of the otolith organ. Kleyn & Lund (1924) and Parker, Pollack & Spoendlin (1965), following Wittmaack's method, destroyed the otoliths by turning a guinea pig on a centrifuge at 2000 revolutions per minute but they were still able to produce caloric reaction, disproving Borries' theory.

Versteegh (1927), Ulrich (1935), Jongkees (1950), Graybiel, Niven & Walsh (1952), Sullivan (1959), and Fernandez, Alzate & Lindsay (1960) denied any appearance of nystagmus after stimulation of the otolith organ, or utricular nerve. On the contrary, Niven, Hixson & Correia (1965), stimulating the otolith organ in human centrifuge, and Jongkees & Philipszoon (1962) and McCabe (1964), by linear acceleration, were able to provoke nystagmus.

Maxwell (1923), Morimoto (1955), Bergstedt (1961), and Owada & Okubo (1963) hypothesized that the otolith system has a regulatory effect upon the cupula ampullaris system.

During this experiment it became apparent that the inhibition or enhancement of caloric nystagmus in the cat can be attributed to the status of mental alertness or to some other mechanisms in which the otolith system could play an important role. By changing the center of gravity and moving the fronto-occipital axis from 45° to 135° angle, the otoliths are hanging freely in the endolymphatic space and provoke traction and maximal physiological stimulus on the macular hair cells. If a caloric test is performed at this angle, which is not the optimal position for the lateral semicircular canal, there is a statistically significant increase in duration of post-caloric nystagmus with no difference in maximum intensity of nystagmus. Therefore, it could be hypothesized that the otolith system has a controlling or regulatory mechanism over post caloric duration of nystagmus through central pathways. Nystagmus duration would increase when the otoliths provoke stronger stimulus on the hair cells. However, if the hypothesis that stimulation of the otoliths could provoke nystagmus is correct, we would have in our experiment a cumulative effect. Simultaneous stimulation of the otoliths (changing the gravity) and of the semicircular canals (caloric test) would increase nystagmus. Another possibility should be taken into consideration also: a significant increase

UNTERSUCHUNGEN ZUR BESTIMMUNG DER MASSGEBENDEN CHARAKTERISTIKA DES ELEKTRONYSTAGMOGRAMMS GESUNDER VERSUCHSPERSONEN VERSCHIEDENEN LEBENSALTERS BEI ROTATORISCHEN BESCHLEUNIGUNGSREIZEN

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Reihenuntersuchungen gesunder Versuchspersonen verschiedenen Lebensalters mittels eines genau definierten rotatorischen Beschleunigungsreizes führten auf Grund der rechnerischen Auswertung der akzeleratorischen postakzeleratorischen und dezeleratorischen postdezeleratorischen Perioden aller registrierten Elektronystagmogramme und nachfolgenden Mittelwertsberechnung, wobei die einzelnen Nystagmusperioden zueinander und miteinander sowie über alle Altersgruppen in ein Verhältnis gesetzt wurden, zur Bestimmung von Frequenz und Amplitude als maßgebende und vergleichbare Charakteristika des experimentellen Nystagmus. Die Amplitude stellt dabei eine quantitative Größe dar, die sinnvoll als Maß für die Intensität eines zeitlich begrenzten Nystagmus herangezogen werden kann. Die Frequenz bildet wahrscheinlich die qualitative Größe, die, wie auf Grund der Untersuchungsergebnisse nachgewiesen wird, als vereinfachender Faktor (Quotient) für die Einzelgrößen Schlagzahl und Nystagmusdauer zur Charakterisierung des Reizeffektes eingeführt werden kann.

Die experimentelle Gleichgewichtsprüfung mittels rotatorischer Beschleunigungsreize unter gleichzeitiger elektronystagmographischer Registrierung des ausgelösten Nystagmus hat zwar grundsätzlich wichtige Erkenntnisse hinsichtlich der Funktionsweise des Vestibularissystems erbracht, erweist sich aber bis heute, insbesonders infolge der immer wieder vorgenommenen Modifikationen der Untersuchungsmethoden, als zu kompliziert für den klinisch-praktischen Gebrauch. Neben der Erkennung und Beseitigung möglicher Fehler des aufgezeichneten Kurvenverlaufes, seien sie nun methodisch oder apparativ bedingt, ist zunächst eine Einigung auf die maßgebenden Charakteristika des Elektronystagmogramms beim Gesunden erforderlich, um pathologische Abweichungen sicher erkennen und vergleichen zu können. Mittermaiers Forderung, daß nur mehrfach wieder-

Herrn Prof. Dr. Dr. h.c. H. Frenzel, Göttingen, gewidmet

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nusregistrierung erfolgte über bitemporal angelegten Elektroden und neutraler Elektrode auf der Stirnmitte mittels eines Siemens Cardirex und Vorverstärker. Zwischen Rechts- und Linksdrehung wurde eine Pause von 8 min eingelegt

In der Gruppe bis zum 10 Lebensjahr wurde wegen der überaus heftigen vegetativen Reaktionen nach plötzlichem Stopp aus voller Drehung von einem ruckartigen Anhalten abgesehen und stattdessen entschleunigt. Diese Altersgruppe wurde daher in alle Kurven, die eine postrotatorische Nystagmusperiode umfassen, nicht eingetragen

Jede Nystagmusperiode (Nystagmus perrotatorius I und II, Nystagmus postrotatorius I und II) der so geschriebenen Elektronystagmogramme wurde bezüglich ihrer Dauer, der Schlagzahl und der Summe der einzelnen Nystagmusamplituden ausgewertet Eine 10°-Blickwinkeleichung gestattete es dabei, die in Millimeter geschriebenen Amplituden auf Winkelgrad zu beziehen Entsprechend der oben angegebenen Altersverteilung wurden die pro Altersgruppe errechneten Mittelwerte in die Diagramme eingetragen

Die erforderlichen umfangreichen rechnerischen Auswertungen wurden an der IBM-7040 im Göttinger Rechenzentrum durchgeführt

ERGEBNISSE

1 Nystagmusdauer und Schlagzahl

Bei der experimentellen Vestibularisprüfung wird der Reizeffekt allgemein durch die Einzelfaktoren *Nystagmusdauer* (T), *Schlagzahl* (N) und *Amplitude* (A) charakterisiert. Alle diese Faktoren weisen individuell und interindividuell und in ihren Relationen zueinander oftmals erhebliche Schwankungen auf (Frenzel, 1954, Fischer, 1928, Mittermaier 1965, Mittermaier & Rossberg, 1956, Mittermaier & Christian, 1954), so daß eine Zusammenfassung zweier oder mehrerer dieser Größen bei der Bewertung der Reaktion, insbesondere aus dem Blickwinkel des Einzelfalles heraus, zunächst unzulässig erscheint Anders verhält es sich dagegen, wenn man errechnete Mittelwerte größerer Untersuchungsreihen, besonders unter Vergleich verschiedener Altersgruppen, zu Grunde legt, da sie Aufschlüsse über die allgemeine biologische Reaktionsweise des geprüften Organes zulassen

Ein Vergleich der Mittelwerte von Dauer und Schlagzahl der von uns aufgezeichneten Elektronystagmogramme zeigte — sieht man einmal von geringfügigen Unterschieden in den 1 perrotatorischen und 1 postrotatorischen Nystagmusperioden ab, in denen die Nystagmusdauer mit steigendem Alter etwas weniger als die Schlagzahl zunahm — ein auffallend ähnliches altersabhängiges Verhalten der zu der gleichen Nystagmusperiode gehörenden Kurvenverläufe Dies legte die Vereinfachung nahe, sie zu einer Größe, nämlich der Frequenz (F), zusammen zu fassen Es ist aber dabei nicht zulässig lediglich die entsprechenden Mittelwerte von N und T ins Verhältnis zu setzen, sondern es muß für jede Versuchsperson die Frequenz in den *einzelnen* Nystagmusperioden berechnet werden Die mittleren Frequenzen pro Altersgruppe stellen sich dann als arythmetische Mittelwerte der individuellen Frequenzen aller dieser Altersgruppe ange-

holte Untersuchungen mit jeweils gleichgerichteten Ergebnissen zur Beurteilung herangezogen werden dürfen, deutet die bestehenden Schwierigkeiten an und läßt den Vergleich von Originalkurven vorerst noch als das zweckmäßigste Vorgehen erscheinen.

Die kritische Bewertung der Mittelwerte von in anderem Zusammenhang mittels rotatorischen Beschleunigungsreizen aufgenommenen Elektronystagmogrammen gesunder Versuchspersonen verschiedenen Lebensalters[1] hinsichtlich der Eignung zu ihrer Charakterisierung zeigte, daß die Nystagmusdauer, die Anzahl der Nystagmusschläge und die Summe der einzelnen Nystagmusamplituden gemeinsam zwar jede Nystagmusperiode[2] für sich beschreiben, aber keinen Vergleich zwischen den verschiedenen Nystagmusperioden erlauben. Dies liegt offensichtlich daran, daß trotz der deutlichen *Altersabhängigkeit der bei gesunden Versuchspersonen gewonnenen* Mittelwerte die genannten Größen (Dauer, Schlagzahl, Schlagweite), wenn man sie in ihrer Gesamtheit betrachtet, für das Nystagmusgeschehen nicht bezeichnend sind. Es wurde daher der Versuch unternommen, auf Grund einer Auszählung jeder Nystagmusperiode der in den einzelnen Altersgruppen aufgezeichneten Elektronystagmogramme bezüglich ihrer Dauer, der Anzahl der Schläge und der Summe der einzelnen Nystagmusamplituden und einer Auswertung der errechneten Mittelwerte zu einer Bestimmung der maßgebenden Charakteristika zu gelangen.

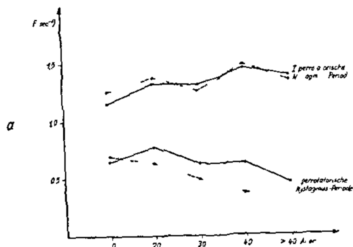
METHODIK

Den Untersuchungen lagen 5 Gruppen zu je 20 Versuchspersonen zu Grunde, die die Altersabschnitte bis zum 10. Lebensjahr, vom 11. bis 20., 21. bis 30., 31. bis 40. sowie 41. bis 65. Lebensjahr umfaßten. Von den insgesamt 100 jeweils mit Rechts- und Linksdrehung registrierten gesunden Personen waren nach kritischer Sichtung nur die Elektronystagmogramme von 89 Probanden, die sich etwa gleichmäßig auf alle Altersgruppen verteilten, für die vorliegenden Untersuchungszwecke verwertbar. Die im folgenden mitgeteilten Ergebnisse ließen aber infolge ihrer bei mehrfachen Überprüfungen, bei denen einheitlich für alle Werte die Gegenrechnung jeweils unterschiedlich angesetzt wurde, regelmäßig erhaltenen gleichförmigen Resultate die Zahl von 89 doppelseitigen Untersuchungen hinsichtlich ihrer Aussagekraft ausreichend erscheinen, so daß von Ergänzungsprüfungen abgesehen wurde.

Die Drehprüfungen wurden unter Verwendung des Siemens-Drehstuhls mit einer Beschleunigung von 3°/sec bis zu einer Endgeschwindigkeit von 90°/sec vorgenommen, die 1 min lang eingehalten und aus der dann plötzlich angehalten wurde. Die bei geschlossenen und verbundenen Augen durchgeführte Nystag-

[1] Es handelt sich hierbei um Reihenuntersuchungen im Rahmen einer an der Universitäts-Hals-Nasen-Ohrenklinik Göttingen durchgeführten Doktorarbeit, deren Ergebnisse bisher noch nicht veröffentlicht wurden.

[2] Im folgenden wurde zum Zwecke der eindeutigen Abgrenzung gegenüber den beiden Phasen eines Nystagmusruckes anstelle der von *Mittermaier* u. a. verwendeten Bezeichnung I und II (inverse) Nystagmus*phase* stets der Begriff Nystagmus*periode* eingesetzt.



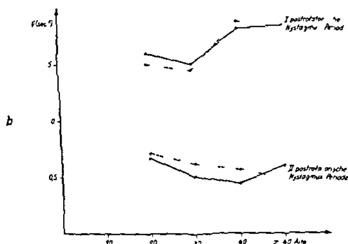


Abb. 1. Abhängigkeit der gemittelten Frequenz vom Alter. perrotatorische Perioden (*a*) postrotatorische Perioden (*b*). Erläuterung im Text. ——— Rechtsdrehung - - - - Linksdrehung

Tabelle 1. *Mittelwerte von Frequenz, Amplitude, Winkelgeschwindigkeit und Amplitude pro Nystagmusschlag für die einzelnen Nystagmusperioden. Erläuterung im Text*

	Nystagmus-Perioden			
	perr. I	perr. II	post. I	post. II
F (sec⁻¹)	1,33	0,5[illegible]	1,6[illegible]	0,58
A (Grad)	374	111	3[illegible]0	101
A/T (Grad/sec⁻¹)	7[illegible]4	1,89	10,9[illegible]	1,6[illegible]
A/N (Grad)	[illegible]7[illegible]	2,[illegible]5	[illegible]23	2,[illegible]4

hörenden Versuchspersonen dar. Relativ zu der über alle Probanden einer Altersgruppe gemittelten Frequenz unterliegen die individuellen Frequenzen dabei keinen größeren Schwankungen als die Nystagmusdauer T und die Schlagzahl N zu ihren entsprechend gemittelten Werten.

Auf Grund der zunächst getrennt vorgenommenen Mittelwertsberechnung der akzeleratorisch-postakzeleratorischen und dezeleratorisch-postdezeleratorischen Komponenten hinsichtlich ihres Verhaltens von Nystagmusdauer und Schlagzahl im Gesamtablauf des Reizeffektes und nachfolgendem Vergleich in den einzelnen Altersgruppen halten wir es daher für berechtigt, T und N als Einzelgrößen zu vernachlässigen und ihren Quotienten, die *Frequenz* (F = N/T), *als maßgebendes Charakteristikum im Kurvenablauf* einzuführen.

2. *Frequenz*

Nach den Untersuchungen von van Egmond, Groen & Jongkees (1952) sowie Mittermaier & Rossberg (1956) kommt den nach einer positiven oder negativen Beschleunigung auftretenden 2. (inversen) Perioden für die Beurteilung des Erregungsgrades bzw. -Ablaufes eine besondere Bedeutung zu. Setzt man die 1. und 2. Perioden der perrotatorischen und postrotatorischen Reaktion miteinander und zueinander in ein Verhältnis, so ergeben sich daraus, wie die Regelmäßigkeit in unseren Untersuchungen erkennen ließ, weitere aufschlußreiche Hinweise für den Erregungsablauf. Voraussetzung dafür ist eine Beschleunigung von mindestens 3°/sec., da erst dann mit einer gewissen Konstanz mit dem Auftreten der 2. inversen Perioden zu rechnen ist (Mittermaier, 1956).

Abbildung 1 zeigt die Abhängigkeit der gemittelten Frequenzen vom Alter. Während in den 1. perrotatorischen und 1. postrotatorischen Perioden die Frequenz offensichtlich mit dem Alter ansteigt, nimmt sie in den entsprechenden Nachreaktionen mit zunehmendem Alter ab. Eine altersbedingte Erhöhung der Frequenz in den 1. Nystagmusperioden wird also regelmäßig von einer altersbedingten Erniedrigung der Frequenz in den Nachreaktionen begleitet. Bemerkenswert ist dabei, daß die Frequenz in den Nachreaktionen stets wesentlich geringer als in den vorangegangenen 1. perrotatorischen bzw. 1. postrotatorischen Nystagmusperioden ist, d. h. also, *für die 1. per- und 1. postrotatorische Nystagmusperiode sind mittelfrequente, für die Nachreaktionen wenig frequente Nystagmusschläge charakteristisch.* Dabei unterscheiden sich die 2. inversen Nystagmusperioden hinsichtlich ihrer Frequenz nur wenig voneinander, während die Frequenz der 1. postrotatorischen Nystagmusperiode etwas höher als die der 1. perrotatorischen liegt (vgl. auch Tab. 1).

In Abbildung 2 sind die Frequenzen der einzelnen Nystagmusperioden miteinander verglichen worden. Für die Darstellung des altersabhängigen Verhaltens wurden hierbei wiederum, entsprechend der Berechnung der Frequenz, zunächst die Quotienten der verschiedenen Frequenzen für jede einzelne Versuchsperson gebildet und anschließend gemittelt.

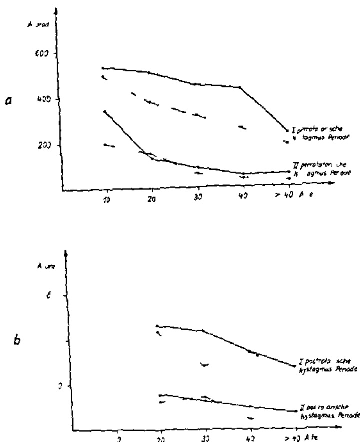


Abb 3 Abhangigkeit der gemittelten Amplitude vom Alter perrotatorische Perioden (a) postrotatorische Perioden (b) Erlauterung im Text ——— Rechtsdrehung Linksdrehung

deutlichen Abnahme der Quotienten mit dem Alter Übertragt man dieses Verhalten auf die oben aufgezeigte mit steigendem Lebensalter eintretende Zunahme der Frequenz in den 1 und Abnahme in den 2 Nystagmus perioden so bedeutet dies *daß die Frequenz der 1 postrotatorischen relativ zur 1 perrotatorischen Periode mit dem Alter starker zunimmt die der 2 postrotatorischen relativ zur 2 perrotatorischen Periode starker abnimmt*

Die Einzelkomponenten der perrotatorischen und postrotatorischen Reaktion auf einen genau definierten Reiz zeigen also im Verhalten ihrer Frequenz ein altersabhangig so regelmaßiges Reizeffektbild daß sich fur die verschieden Altersgruppen jeweils festlegbare Großen ergeben Die vorausgenommene vereinfachende Zusammenfassung von Dauer und Schlagzahl zu dem Begriff der Frequenz als eines maßgebenden Charakteristikums im physiologischen Nystagmusablauf wird somit in seiner Berechtigung bestatigt

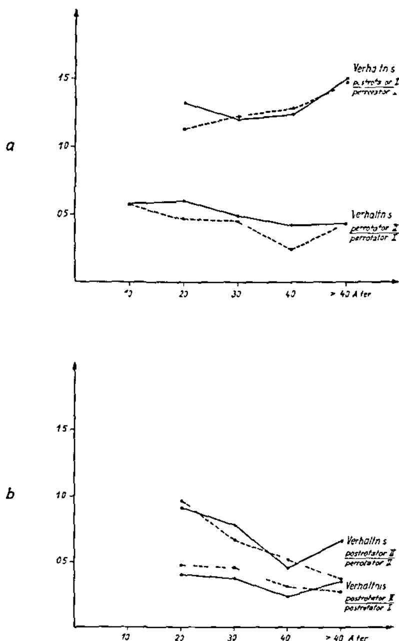


Abb. 2*a* und *b*. Vergleich der Frequenzen der einzelnen Nystagmusperioden zu- und miteinander. ———, Rechtsdrehung; - - - -, Linksdrehung.

Die Gegenüberstellung der Nachreaktionen mit den vorangegangenen Nystagmusperioden läßt erkennen, daß die Quotienten von Postrotatorius II zu Postrotatorius I in der Regel etwas niedriger sind als die von Perrotatorius II zu Perrotatorius I. Mit anderen Worten: *Der Frequenzunterschied zwischen postdezeleratorischer und dezeleratorischer Komponente des Nystagmus ist größer als der zwischen postakzeleratorischer und akzeleratorischer.* Darauf deutete bereits der Kurvenverlauf in Abbildung 1 hin.

Der Vergleich von Postrotatorius I mit Perrotatorius I führt zu einer deutlichen Zunahme, der von Postrotatorius II mit Perrotatorius II zu einer

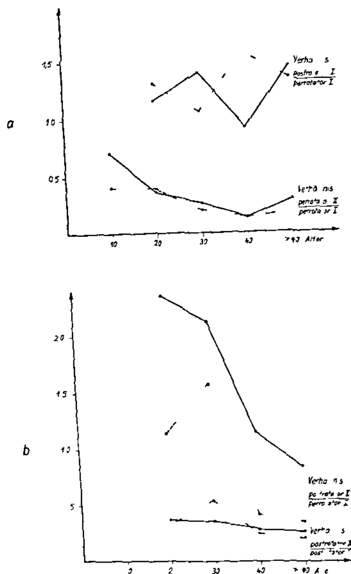


Abb. 4 a und b. Vergleich der Amplituden der einzelnen Nystagmusperioden zu- und miteinander. —— Rechtsdrehung Linksdrehung

Auch bezüglich der Amplitude ließ sich also auf einen genau definierten rotatorischen Beschleunigungsreiz für die akzeleratorischen-dezeleratorischen und postakzeleratorischen-postdezeleratorischen Komponenten zu- und miteinander ein so regelmäßiges Verhalten nachweisen, daß sie als *weiterer* maßgebender Faktor zur Charakterisierung des Reizeffektes angesehen werden muß.

3. *Amplitude*

In Anlehnung an Jung & Mittermaier (1939) sowie Rossberg (1955) soll unter Amplitude im folgenden stets die Summe aller Einzelamplituden in Winkelgrad der während einer Nystagmusperiode registrierten Nystagmusschläge verstanden werden.

Im Gegensatz zur Frequenz nimmt die Amplitude in allen während der Drehprüfung auftretenden Nystagmusperioden mit steigendem Lebensalter ab. Der Vollständigkeit halber ist diese Altersabhängigkeit der Amplitude in Abbildung 3 dargestellt. Berücksichtigt wurde dabei nur die für jeweils alle Versuchspersonen einer Altersgruppe gemittelte Schlagweite. Ebenso wie *die Frequenz ist auch die Amplitude in den Nachreaktionen wesentlich* geringer als in den vorangegangenen 1. per- bzw. postrotatorischen Nystagmusperioden.

In Tabelle 1 sind neben den über Rechts- und Linksdrehung und alle Altersgruppen gemittelten Frequenzen (Abb. 1) und Amplituden (Abb. 3) noch die entsprechenden Winkelgeschwindigkeiten A/T und Amplituden pro Nystagmusschlag A/N eingetragen. Es handelt sich dabei allerdings nur um arythmetische Mittelwerte der altersabhängig errechneten Mittelwerte und nicht um solche der 89 Versuchspersonen, da die Verteilung der Probanden auf die einzelnen Altersgruppen nicht in jedem Falle gleich groß war.

Trotz der relativ geringen Zahl der untersuchten Personen stimmen in gleicher Weise wie bei der Frequenz die in der beschriebenen Form gemittelten Amplituden der 2. perrotatorischen und 2. postrotatorischen Nystagmusperiode praktisch überein. Im Gegensatz zur Frequenz ist aber die Amplitude der 1. perrotatorischen Nystagmusperiode etwas größer als die der 1. postrotatorischen.

Abbildung 4 zeigt einen Vergleich der Amplituden der einzelnen Nystagmusperioden miteinander. Wiederum wurden zunächst alle registrierten Nystagmogramme einzeln ausgewertet und erst dann alle so errechneten Quotienten in den jeweiligen Altersgruppen gemittelt. Dabei erwies sich, daß *zwischen Nachreaktion und vorangegangener Nystagmusperiode bei Postrotatorius II und Postrotatorius I praktisch in allen Altersgruppen ein festes Verhältnis von etwa 1 : 3* besteht, denn die entsprechende Kurve zeigt fast keine Altersabhängigkeit. Dagegen sinkt der Quotient von Perrotatorius II zu Perrotatorius I mit dem Alter ab, d. h. also *daß die Amplitude der 2. perrotatorischen Nystagmusperiode mit zunehmendem Alter deutlich kleiner wird als die der 1. perrotatorischen Periode.* Noch stärker fällt die Amplitude der 2. postrotatorischen relativ zu der der 2. perrotatorischen Nystagmusperiode ab.

Der Vergleich von 1. postrotatorischer und 1. perrotatorischer Nystagmusperiode ergab eine so starke, wahrscheinlich auf die geringe Anzahl der Versuchspersonen zurückzuführende Diskrepanz der Amplitude von Rechts- und Linksdrehung, daß diese Ergebnisse nicht verwertet werden konnten.

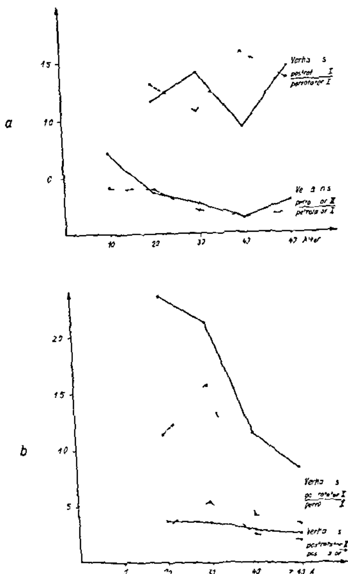


Abb. 4 a und b Vergleich der Amplituden der einzelnen Nystagmusperioden zu und le nach der —— Rechtsdrehung Linksdrehung

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TABELLE 2. *Schematische Darstellung der Altersabhängigkeit von Frequenz und Amplitude (Pfeilrichtung ↑ bedeutet Zunahme, Pfeilrichtung ↓ Abnahme von Frequenz bzw. Amplitude.)*

	Nystagmus-Perioden			
	perr. I	perr. II	post. I	post. II
F	↑	↓	↑	↓
A	↓	↓	↓	↓

keit aufzeigt — *voneinander unabhängigen Größen bilden.* Diese Tatsache soll durch die nachfolgende Tabelle 2, in der zusammenfassend die Abhängigkeit der Amplitude und Frequenz vom Alter eingezeichnet wurde, noch einmal hervorgehoben werden. Die Amplitude stellt danach in allen Perioden des Nystagmusablaufes eine quantitative Größe dar, die, wie Dohlman (1935), Jung (1948) sowie Mittermaier (1954) schon fanden und unsere Untersuchungen jetzt erneut bestätigen konnten, ein gutes Maß für die Intensität eines zeitlich begrenzten Nystagmusgeschehens abgibt. Da man voraussetzen kann, daß bei einer Nystagmusbewegung der Augen eine gewisse Arbeit gegen eine hier nicht näher zu definierende Kraft zu leisten ist, so wird die dazu benötigte Energie in erster Näherung proportional der Winkelauslenkung der Augen sein. Summiert man also die Amplituden aller Nystagmusschläge zeitlich begrenzter Nystagmusperioden auf, d. h. geht zu der eingangs definierten Amplitude über, so kann man diese in erster Näherung proportional zu der während dieser Periode umgesetzten Energie ansehen und damit auch als Maß für die Intensität sinnvoll heranziehen.

Auf die Frequenz als zweite maßgebende Größe des experimentellen Nystagmus soll hier noch nicht näher eingegangen werden, da weitere Untersuchungen zur genaueren Erfassung ihrer Bedeutung im Reaktionsablauf noch nicht abgeschlossen sind.

SUMMARY

Serial investigations of healthy persons of different ages by means of a strictly defined rotatory accelerating stimulus through mathematical evaluation of the acceleratory, postacceleratory and deceleratory postdeceleratory periods of all the registrated electronystagmograms following mean calculation—whereby the separate nystagmus periods are put in relation to each other and put together as well in all age groups—lead to a determination of the frequency and of the amplitude as authoritative and comparable characteristics of the experimental nystagmus. The amplitude thereby represents a quantitative measure which logically becomes a measure of the intensity of a limited nystagmus. The frequency probably constitutes the qualitative measure and can be introduced as

4 *Amplitude und Frequenz*

Aus den vorliegenden Untersuchungsergebnissen leitete sich nunmehr die Frage ab, ob es für zeitlich begrenzte Nystagmusperioden, wie sie bei der Dreherregbarkeitsprüfung oder auch bei der thermischen Labyrinthprüfung zu beobachten sind, möglich ist, eine einzige charakterische Größe für den Reaktionsablauf zu finden Dieser Versuch ist an sich nicht neu und wurde erstmalig von Ohm (1939) unternommen, der aus dem Produkt von Amplitude × Frequenz ein Maß für die „Energie" des Nystagmus ableiten zu können glaubte

Wir haben ebenfalls versucht, die Amplitude (A) und die Frequenz (F) in der Form A × F bzw A/F zu verknüpfen A/F zeigte dabei in den Nachreaktionen eine steile Altersabhängigkeit und verlief in den 1 Nystagmusperioden ähnlich wie die Amplitude selbst A × F verhielt sich sogar in allen Nystagmusperioden bezüglich der Altersabhängigkeit ähnlich wie die Amplitude Beide Kombinationen vermitteln also scheinbar keinen besseren Aufschluß über den Reaktionsablauf als die Amplitude Von der Einführung einer dieser beiden Verknüpfungen als Intensitätsgröße muß aber abgesehen werden, weil ein Vergleich zweier Nystagmusperioden mit gleicher Amplitude, aber verschiedener Frequenz zu unbefriedigenden Ergebnissen führt

Ähnlich liegen die Verhältnisse, wenn man die Quotienten A/N und A/T betrachtet und die Frequenz als solche einmal unberücksichtigt läßt Diese Größen verhalten sich mit zunehmendem Alter zwar wiederum praktisch wie die Amplitude und zeigen nach entsprechenden Vergleichen auch ein ähnliches Kurvenbild wie Abbildung 4, in der die Amplitudenverhältnisse verschiedener Nystagmusperioden dargestellt sind, jedoch verdeutlicht die Gegenüberstellung zweier verschiedener Nystagmusperioden sogleich die Unmöglichkeit derartiger Kombinationen Multipliziert man nämlich die mittlere Amplitude pro Nystagmusschlag (A/N) bzw die mittlere Winkelgeschwindigkeit (A/T) nur im Zähler und Nenner mit derselben beliebigen Zahl und zeichnet sich dies für zwei verschiedene Fälle auf, dann erkennt man, daß etwas grundsätzlich Unterschiedliches trotz gleicher mittlerer Amplitude pro Nystagmusschlag bzw gleicher Winkelgeschwindigkeit vorliegt

In Tabelle 1 sind die beiden Größen A/N und A/T als Mittelwerte über Rechts- und Linksdrehung und über alle Altersgruppen eingetragen Sie zeigen in diesem Fall ein ähnliches Verhalten wie Frequenz und Amplitude

SCHLUSSBETRACHTUNG

Nach den im Vorliegenden mitgeteilten Untersuchungsergebnissen halten wir die Folgerung für berechtigt *daß die Amplitude und die Frequenz für den Ablauf des experimentellen Nystagmus ausschließlich die zwei charakteristischen, aber* — wie ihre zum Teil unterschiedliche Altersabhängig-

QUANTITATIVE CYTOCHEMICAL ASPECTS ON THE MECHANISM OF CENTRAL COMPENSATION AFTER UNILATERAL VESTIBULAR NEUROTOMY

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Three groups of rabbits were subjected to right sided vestibular neurotomy. The animals of the first group were sacrificed 5 days after operation, the others after 15 and 30 days respectively. Bilateral samples of isolated Deiters' giant nerve cells from the lateral vestibular nuclei were analyzed on total amount of RNA and succinoxidase activity. Bilateral samples of Purkinje cells from lobulus III hemisphere were analyzed on total amount of RNA.

The succinoxidase activity in Deiters' cells showed an increase both in the left and right side compared with controls in the groups where the rabbits were killed 5 and 15 days after neurotomy. In these animals the right side had a higher activity than the left and this side difference had its maximum 15 days after the operation. The rabbits killed 30 days after neurotomy showed no increased succinoxidase activity in either side compared with controls.

The total RNA in Deiters' cells did not significantly differ either between left and right side or compared with *controls*. The rabbits tested for total RNA in Deiters' cells were killed 15 and 30 days *after neurotomy* respectively. The total RNA amount of the Purkinje cells is significantly higher in the left side compared with the right (operated) side in all three groups.

The observations suggest that the cerebellum has a *more permanent* functional asymmetry after unilateral labyrinthectomy than the vestibular nuclei as measured with cytochemical methods. Observations on Deiters' nucleus indicate a possible difference between RNA and succinoxidase activity during changed cell function.

INTRODUCTION

Long term observations on patients after unilateral labyrinthectomy show that the first phase with spontaneous nystagmus towards the intact side has subsided after about one month (Fluur 1961). Experimental studies on rabbits indicate an even shorter time for this phase (Hallén & Hamberger 1964).

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simplifying factor (quotient) of the particular measures of nystagmus duration and pulsation in characterizing the irritating effect. This is demonstrated by the findings.

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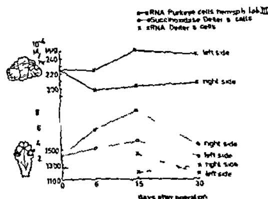


Fig. 1. Summary of the RNA and succinoxidase activity results, correlation of observations and time after neurotomy.

bedded in paraffin and cut at 50 μ. Single nerve cells were isolated by micromanipulation from the sections and extracted with ribonuclease in an oil chamber. The extracts were collected, evaporated and redissolved in a glycerol-containing buffer forming lens-shaped drops. The ultraviolet absorption at 257 mμ was determined by a photometric system (Edström 1953).

Succinoxidase activity determinations

The microdissection technique of Hydén (Hydén & Pigon 1960) was used for the nerve cells and the oxygen consumption was measured with Zeuthen's micro diver technique (Zeuthen 1953). Isolated nerve cells and spherical clumps of glial cells were introduced into separate micro divers with about 0.5 μl of the incubation medium. Oxygen consumption was determined manometrically for 2–3 hours and was expressed as 10^{-4} μl O_2 per sample and hour.

RESULTS

Deiters cells

The RNA results of the content is presented in Table 1. As illustrated in Fig. 1 the amount of RNA is slightly lowered on the operated (right) side two weeks after operation but increases to that of the controls in the 30 day group. The left side, on the other hand, seems to contain nerve cells with a higher content of RNA after two weeks but is also close to the controls at the end of the time studied.

The succinoxidase activity (Table 2) of the Deiters cells increases with time in a similar way on both sides, although the changes on the operated side are considerably larger. In the group analysed 30 days after operation none of the sides differ significantly from the controls.

ponderance against the intact side. These observations have been made as late as eight years after the labyrinthectomy (Aschan, Bergstedt & Stahle, 1956).

In an earlier report (Hallén & Hamberger, 1964) the large nerve cells of the lateral vestibular nuclei of both sides in rabbits were analyzed with respect to the activity of a respiratory enzyme, succinoxidase. Two weeks after unilateral vestibular neurotomy a definite side difference was established with respect to the enzyme activity.

Electrophysiological works have demonstrated the important role of the cerebellum in the coordination of the motor activity and also in the regulation of the spontaneous activity of the vestibular nuclei (DeVito, Brusa & Arduini, 1956). With respect to this an unsymmetrical reaction within the cerebellum would be expected after unilateral vestibular neurotomy.

We have analyzed the RNA content of the Purkinje cells in the hemisphere lobe III on both sides. This part of cerebellum is closely related to vestibular structures as judged from cytochemical observations (Jarlstedt, to be published). The RNA content and the succinoxidase activity of the large neurons of the lateral vestibular nuclei have been measured on the same animals.

Analyses have been made 1, 2 and 4 weeks after unilateral neurotomy. Thus the reactions in different loci are recorded during the acute phase of vestibular compensation. The more long-lasting changes in the chemical constituents of the nerve cells probably remain during the rest of the life of the unilaterally labyrinthectomized individual.

MATERIAL AND METHODS

White rabbits of both sexes weighing 1.5–1.8 kg were used. Deiters' giant nerve cells from the right and left lateral vestibular nucleus and in some measurements of succinoxidase activity also the surrounding glial cells were analyzed for both RNA content and succinoxidase activity. Purkinje cells from right and left hemisphere lobe III of cerebellum were determined with respect to RNA content.

Vestibular neurotomy

Vestibular neurotomy was performed as reported in an earlier study (Hallén & Hamberger, 1964). In the anaesthetized animal the bone was drilled away in a small area above the atlanto-occipital membrane. The dura was incised and the division of the vestibular portion of the eighth nerve was made in the porus acusticus internus dx.

RNA determinations

Pieces of cerebellum and medulla oblongata were removed immediately after death and fixed in Carnoy's solution. The tissue samples were em-

TABLE 3 *Determinations of RNA in Purkinje cells taken from hemisphere, lobulus III*

Determinations carried out on samples of two cells

Rabbit	Mean value in μμg Left	n	± S E M Right	n	Percentage higher on the left side
(a) 5 days after section of the right vestibular nerve					
1	185 ± 6 0	6	161 ± 8 2	6	14 9
2	218 ± 13 8	6	162 ± 11 8	6	34 6
3	250 ± 12 1	6	239 ± 14 0	6	4 6
4	239 ± 5 7	6	227 ± 9 6	6	5.3
	P value for the whole material P < 0 01				
(b) 15 days after section of the right vestibular nerve					
1	241 ± 11 7	6	202 ± 9 0	6	19 3
2	264 ± 4 1	6	213 ± 17 7	6	23 9
3	239 ± 5 4	6	191 ± 12 4	6	25 1
	P value for the whole material P < 0 001				
(c) 30 days after section of the right vestibular nerve					
1	246 ± 15 7	6	198 + 14 4	6	24 2
2	220 + 5 5	6	198 ± 15 8	6	11 1
3	283 + 10 7	6	245 ± 15 4	6	15 5
4	230 + 6 8	6	188 ± 9 8	6	22 3
	P value for the whole material P < 0 01				

DISCUSSION

The clinical investigations on the compensatory mechanisms after unilateral labyrinth destruction are mainly based on the reactions observed by cold and warm water irrigation of the intact labyrinth The interest is to a great deal focussed on the possible activity levels of the vestibular nuclei modified by changed input from the intact peripheral organ (Cawthorne, Fitzgerald & Hallpike, 1942 Aschan Bergstedt & Stahle 1956 van Eyck 1956

Experimental work have indicated that the type of nystagmus which appears immediately after unilateral labyrinthine destruction is initiated in the vestibular nuclei decerebration decerebellation and despinalisation being without effect (Magnus 1924 Demetriades & Spiegel 1925) The authors conclude that the vestibular nuclei of the labyrinthectomized side become hypersensitive in order to compensate for the loss of labyrinthine impulses These conclusions are drawn from the observations that if the labyrinth of the earlier saved side is destroyed some days after the first operation a spontaneous nystagmus is evoked towards the initially operated side The part played by the cerebellum in this connection is of great in

TABLE 1. *Determinations of RNA in Deiters' giant nerve cells of the lateral vestibular nucleus of the rabbit*

Determinations carried out on samples of 1–4 cells

Rabbit	Mean value in μμg ± S.E.M. per cell: Left	n	Right	n
(a) 15 days after section of the right vestibular nerve				
1			1350 ± 41	10
2	1261 ± 81	12	1275 ± 95	11
3	1179 ± 90	10	853 ± 52	10
4	1180 ± 55	12	935 ± 36	9
5	1285 ± 74	10	1327 ± 124	12
6	1754 ± 132	9	1408 ± 138	11
7	1615 ± 111	10	1161 ± 67	14
(b) 30 days after section of the right vestibular nerve				
1	1396 ± 68	11	1566 ± 65	15
2	1245 ± 75	10	967 ± 49	13
3	1081 ± 49	14	1384 ± 132	9
4	958 ± 98	6	1136 ± 90	6
5	1224 ± 158	3	1399 ± 48	5

Purkinje cells

The RNA amount of the Purkinje cells (Table 3) show changes parallel to those of the RNA of the Deiters' cells during the first two weeks, i.e. a decrease on the right (operated) and an increase on the left side. However, this side difference seems to be of a more permanent nature than that observed with the Deiters' cells.

TABLE 2. *Effect of vestibular neurotomy on succinoxidase activity in Deiters' giant nerve cells*

Expressed as 10^{-4} μl O_2/hr

	Nerve cell	p
Mean time after neurotomy 5 days. No. of animals 5		
Right side (neurotomy)	5.6 ± 0.7	< 0.05
Left side (control)	3.1 ± 0.7	
Mean time after neurotomy 15 days. No. of animals 9		
Right side (neurotomy)	7.9 ± 1.8	< 0.05
Left side (control)	4.0 ± 0.7	
Mean time after neurotomy 30 days. No. of animals 5		
Right side (neurotomy)	3.6 ± 0.8	
Left side (control)	1.9 ± 0.6	

the vestibular nuclei of the operated side which is initially lowered but later returns to the normal, i.e. the curve of the RNA content. On the other hand, the creation of a state of hypersensitivity to different, subliminal impulses as a compensation for the loss of normal labyrinthine impulses, a mechanism suggested by several authors, as mentioned above, would be supposed to require an increased energy supply during the acute phase, i.e. the curve of the succinoxidase activity.

If the suggested hypothesis is valid in these connections, the results of the RNA content of the Purkinje cells reflect a more permanent functional asymmetry in a part of the cerebellum after unilateral labyrinthectomy. As the great part of electrophysiological data attribute an inhibitory action of cerebellum on the vestibular nuclei, and as it has been shown that the presence of an intact cerebellum is a prerequisite for vestibular compensation, it is well in line that the side difference obtained in the results would give an increased inhibition on the intact side and the reverse on the labyrinthectomized side.

In summarizing, the present results give quite strong indications that the cerebellum is an important coordinator of the vestibular system and that the more long lasting responsibility for a vestibular compensation resides in this organ.

ZUSAMMENFASSUNG

Drei Gruppen von Kaninchen wurden rechtsseitiger Vestibularisneurotomie unterzogen. Die erste Gruppe von Tieren wurde 5 Tage nach der Operation getötet, die anderen 15 beziehungsweise 30 Tage nach der Operation.

Bilaterale Proben von Deitersschen Riesenzellen vom lateralen Vestibulariskern wurden auf die totale Menge RNA und Succinoxydaseaktivität hin analysiert. Bilaterale Proben von Purkinjeschen Zellen vom III. Lobulus, Hemisphäre, wurden mit Hinsicht auf die Totalmenge RNA analysiert.

Die Succinoxydaseaktivität in den Deitersschen Zellen zeigte eine Steigerung sowohl für die rechte als auch für die linke Seite, verglichen mit Kontrollen in den Gruppen, in denen die Kaninchen 5 und 15 Tage nach der Nervendurchtrennung getötet wurden. Bei diesen Tieren zeigte die rechte Seite eine höhere Aktivität als die linke Seite. Dieser Seitenunterschied erreicht sein Maximum 15 Tage nach der Operation. Die Kaninchen, die 30 Tage nach der Nervendurchtrennung getötet wurden, zeigten keine erhöhte Succinoxydaseaktivität, weder rechts- noch linksseitig verglichen mit Kontrollen.

Die totale Menge RNA in den Deitersschen Zellen unterschied sich nicht bedeutend, weder zwischen rechter und linker Seite oder verglichen mit den Kontrollen. Die Kaninchen, die mit Hinsicht auf die RNA-Menge in diesen Zellen untersucht wurden, wurden 15 beziehungsweise 30 Tage nach der Operation getötet.

Die Totalmenge RNA in den Purkinjeschen Zellen war bedeutend grösser auf der linken Seite im Vergleich zu der rechten (operierten) Seite in allen 3 Gruppen. Diese Beobachtungen deuten an, dass das Cerebellum eine mehr fort

terest, although it does not abolish the immediate destructive nystagmus, it is a necessity for the subsiding of the nystagmus during the weeks after labyrinthectomy.

When the present data are taken in consideration with the cited experiences as background there are some points of possible correlation. It is evident that both the RNA content and the succinoxidase activity of the Deiters' cells of the operated side are close to those of the controls at the end of the acute phase of vestibular compensation. This corresponds with a functionally well restituted animal at the same time. A striking difference between the two chemical functions of the nerve cells is that the RNA content is constant or decreased during the middle of the compensation phase (15 days after operation) while the succinoxidase activity is highly increased. The Purkinje cells of cerebellum also develop a side difference with respect to the RNA content, namely a lowered amount on the operated side and the reverse on the other side. The changed balance between the two sides is not subsiding at the end of the period, probably reflecting a more permanent state in the compensating animal.

Before further discussion of the interpretation of the present data, an evaluation of RNA content and succinoxidase activity as parameters of nerve cell function is necessary. It is well known from physiological investigations of intact animals that the glucose consumption and respiration increase as a result of increased function, either due to motor activity or sensory stimulation. The total RNA has also been shown to increase during similar conditions (Geiger, 1957). The RNA content and succinoxidase activity in single nerve cells have been shown to increase during conditions implying increased neuronal function in several works from this laboratory (Hydén & Pigon, 1960). The electron microscopical investigations, demonstrating an increase in mitochondrial size and in the number of RNA containing structures shortly after sensory stimulation, are other evidences supporting this interpretation (Chentsov, Borovjagin & Brodskij, 1961).

In those investigations where RNA and a respiratory enzyme have been studied on the same material, the changes of both have always been fairly parallel although the respiratory enzymes generally develop more striking changes (Hydén & Pigon, 1960, Blomstrand, Hallén, Hamberger & Jarlstedt, to be published). In the present results on the Deiters' cells a constant or decreased RNA content is found in cells showing an increased succinoxidase activity. These data indicate a difference between RNA and succinoxidase activity during changed cell function.

In order to try to define the natures of a possible differentiation of cell function, it is important to return to the state of activity of the central vestibular system in the animal. During the acute state of vestibular compensation after labyrinthectomy, the animal has a falling tendency to the operated side which towards the end of the phase more and more subsides. These observations can be correlated to a state of activity of the cells in

ÜBER DEN EINFLUSS DES OHRPASSTÜCKES AUF DEN FREQUENZGANG DER SCHALLÜBERTRAGUNG VOM HÖRER ZUM TROMMELFELL (MODELLVERSUCHE AM KÜNSTLICHEN OHR)

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Es wird festgestellt, daß durch das Verbindungsstück zwischen Hörer und Gehörgang die Übertragungseigenschaften eines Hörgerätes verändert werden können. Ein unzweckmäßig gebohrtes Ohrpaßstück kann den besten Breitbandhörer wirkungslos machen, wie das Beispiel mit dem trichterförmigen Kanal, dessen engste Stelle zum Trommelfell zeigt, veranschaulicht. Ebenso ist es möglich, in *einzelnen Fällen bei extrem* weiten Gehörgängen durch besonders lange Ohrpaßstücke *eine* verbesserte Schallübertragung auch im hohen Frequenzbereich zu erzielen. Diese Verbesserungen können bis zu 10 dB gegenüber einem normalen Ohrpaßstück betragen.

Es ist sowohl für den Hörgerätehersteller als auch für den Hörgerätebenutzer von *großem Interesse*, daß ein möglichst großer Anteil der mit der elektrischen Hilfsenergie verstärkten Schallschwingungen *in — für den Schwerhörigen nutzbare —* Schallenergie umgewandelt wird. Um dieses Ziel zu erreichen, muß sich der Hörgerätekonstrukteur bemühen, Verstärkerschaltungen und elektroakustische Wandler *mit möglichst gutem* Wirkungsgrad zu entwickeln. Es *muß* weiterhin dafür gesorgt werden, daß auf dem Wege von der Hörermembran zum *Trommelfell oder*, falls dieses zerstört sein soll, zur Paukenhöhle nur wenig *von der akustischen* Energie verlorengehen kann. Die *Verluste auf* diesem Energietransport werden im wesentlichen durch das Ohrpaßstück, das zur dichten Verbindung von dem Hörer mit dem Gehörgang dient, beeinflußt.

Die Frage der Frequenzbandbegrenzung durch Hörerankopplung an das Ohr wurde von Güttner (1954) *experimentell* und theoretisch behandelt. In Bezug auf die Ausdehnung des Ohrpaßstückes war schon damals an 2 Typen auf Unterschiede in der Hörausbeute hingewiesen worden, *die bestehen, wenn* die Abdichtung unmittelbar *am Gehörgangseingang* oder mittels des eindringenden Zapfens tiefer im Gehörgang erfolgt. In vereinfachter Form läßt sich *dieser* zwischen Trommelfell und dichtsitzendem Einsteckhörer eines Hörgerätes ablaufende physikalische Vorgang mit einem hol-

während funktionelle Asymmetrie als die Vestibulariskerne nach unilateraler Labyrintektomie aufweist, gemessen mit cytochemischen Methoden

Die Untersuchungen des Nucleus Deiter deuten einen möglichen Unterschied *zwischen RNA und Succinoxydaseaktivität während veränderter Zellfunktion an*

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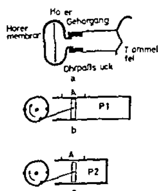


Abb. 1. Abhängigkeit des zu erzielenden Wechseldruckes von dem Volumen verschiedener Druckkammersysteme. (*a*) Druckkammersystem bestehend aus Hörer mit dicht sitzendem Ohrpaßstück, Gehörgang und Trommelfell. (*b*) Druckkammersystem bestehend aus Kolbenpumpe mit großem Zylinder. (*c*) Druckkammersystem bestehend aus Kolbenpumpe mit kleinem Zylinder.

tion des Ohrpaßstückes übernahmen und den künstlichen Gehörgang luftdicht abschlossen. Diesem Hörer wurde eine konstante Wechselspannung mit kontinuierlich veränderlicher Frequenz zugeführt (Tonfrequenzanalysator FTA BN 48302 mit Mitlaufgenerator BN 483011 der Firma Rohde & Schwarz), während die Schwingungen der Mikrophonmembran von einem Mikrophonverstärker (*Brüel & Kjaer Type 2603*) verstärkt und über den Tonfrequenzanalysator dem Gleichspannungsschreiber (ZSG BN 18531 der Firma Rohde & Schwarz) zur Registrierung zugeführt wurden. Die registrierte Gleichspannung ist als ein Maß für den vor der Mikrophonmembran herrschenden Wechseldruck anzusehen, wobei der maximal auftretende Schalldruck mit 0 dB bezeichnet wurde. Minus 20 dB bedeutet beispielsweise einen um 20 dB schwächeren Schalldruck als der maximal auftretende Wechseldruck.

Der Widerstand des Systems Hörer und Gehörgang mit eingelagertem Ohrpaßstück läßt sich durchaus berechnen. Zur Bestimmung des Einflusses

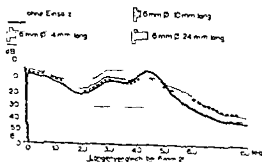


Abb. 2. Einfluß verschieden langer Ohrpaßstücke mit gleichem Kanaldurchmesser auf den Schalldruckverlauf im künstlichen Ohr

ben in einem geschlossenen Zylinder vergleichen (Abb. 1 *b* und 1 *c*), unter der Annahme, daß das Trommelfell zunächst starr und bei den auftreten den Druckänderungen unbeweglich sei. Dem Kolben in den Systemen 1 *b* und 1 *c* kommt die Rolle der Hörermembran 1 *a* zu. Die Luftdruckschwankungen in dem System 1 *b*, in dem die Luft rhythmisch um ein Drittel ihres Volumens zusammengedrückt wird, sind ihrer Amplitude nach kleiner als in dem System 1 *c*, in dem die Kompression auf die Hälfte bei jeder Umdrehung stattfindet. In der Übertragung dieses sinnbildlichen Vergleiches auf das Hören ergibt sich, daß ein Hörer bei gleichem Membranausschlag *einen um so größeren Wechselschalldruck im Gehörgang erzeugen kann*, je kleiner das Gehörgangsvolumen ist. Hierbei soll stillschweigend vorausgesetzt werden, daß der so erzeugte Druck im Gehörgang ohne Rückwirkung auf die Bewegungsamplitude der Hörermembran bleibt.

Die theoretisch zur Hörverbesserung zu fordernde Verkleinerung des Volumens zwischen Trommelfell und Hörer läßt sich praktisch nur unter Einlagerung eines Ohrpaßstückes erreichen, zumal die heutigen Hörer noch zu groß sind, um sie ganz in den Gehörgang einführen zu können. Mit dem Einbringen des Ohrpaßstückes andererseits müssen aber die von der Hörermembran oder von dem Kolben in den Systemen 1 *b* und 1 *c* verdrängten Luftteilchen durch einen engen Querschnitt — den Bohrkanal des Ohrpaßstückes — ausweichen, was bei gleichbleibendem Verdrängungsvolumen mit abnehmendem Querschnitt einen Anstieg der Geschwindigkeit der in dem Rohr hin und her bewegten Luftteilchen zur Folge hat. Hinzu kommt, daß in einem engen Rohr eine viel größere Anzahl von bewegten Luftteilchen mit der Rohrwandung in Berührung tritt als in einem weiten Rohr, so daß beim Schallenergietransport durch ein enges Rohr wegen der höheren Reibung und auch wegen der auftretenden größeren Beschleunigungen weitaus stärkere Verluste zu erwarten sind als in weiten Rohren. Der Vorteil des zu erzielenden höheren Schalldruckes auf Grund des kleinen Volumens wird teilweise wieder aufgehoben durch die eben genannten Verluste, die mit steigender Frequenz, d. h. mit häufigerem Hin- und Hergang der Teilchen je Zeiteinheit zunehmen.

Zur Klärung der Frage, inwieweit durch Länge und Weite der Luftkanalbohrung im Ohrpaßstück das Volumen und seine Rückwirkung auf das Hören beeinflußt werden kann, haben wir Versuche an einem künstlichen Ohr vorgenommen (Brüel & Kjaer Type 4151). Der Gehörgang wurde durch ein Rohr mit einer Bohrung von 10 mm Durchmesser und einer Länge von 24 mm simuliert und das Trommelfell durch die Membran eines Kondensatormikrophones (Brüel & Kjaer Type 4132) dargestellt. In der Versuchsanordnung wurde berücksichtigt, daß die Mikrophonmembran, die einen Durchmesser von 22,7 mm besaß, dem Rohr mit 10 mm Durchmesser nicht *direkt aufsitzt*, so daß sich mit dem vor dem Mikrophon befindlichen zusätzlichen Volumen ein Gesamtinhalt des Gehörganges wie beim Menschen mit 2,5 cm³ ergab. Der Hörer eines Taschenhörgerätes (PHP VII) wurde mit verschiedenen Plexiglaskörpern benutzt, welche die Funk-

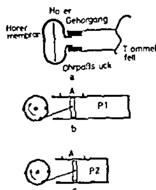


Abb 1 Abhängigkeit des zu erzielenden Wechseldruckes von dem Volumen verschiedener Druckkammersysteme (a) Druckkammersystem bestehend aus Horer mit dichtsitzendem Ohrpaßstuck Gehörgang und Trommelfell (b) Druckkammersystem bestehend aus Kolbenpumpe mit großem Zylinder (c) Druckkammersystem bestehend aus Kolbenpumpe mit kleinem Zylinder

tion des Ohrpaßstuckes ubernahmen und den kunstlichen Gehorgang luftdicht abschlossen Diesem Horer wurde eine konstante Wechselspannung mit kontinuierlich veranderlicher Frequenz zugefuhrt (Tonfrequenzanalysator FTA BN 48302 mit Mitlaufgenerator BN 483011 der Firma Rohde & Schwarz) wahrend die Schwingungen der Mikrophonmembran von einem Mikrophonverstarker (Bruel & Kjaer Type 2603) verstarkt und uber den Tonfrequenzanalysator dem Gleichspannungsschreiber (ZSG BN 18531 der Firma Rohde & Schwarz) zur Registrierung zugefuhrt wurden Die registrierte Gleichspannung ist als ein Maß fur den vor der Mikrophonmembran herrschenden Wechseldruck anzusehen wobei der maximal auftretende Schalldruck mit 0 dB bezeichnet wurde Minus 20 dB bedeutet beispielsweise einen um 20 dB schwacheren Schalldruck als der maximal auftretende Wechseldruck

Der Widerstand des Systems Horer und Gehorgang mit eingelagertem Ohrpaßstuck laßt sich durchaus berechnen Zur Bestimmung des Einflusses

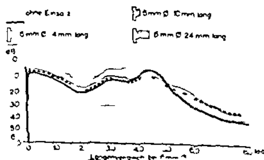


Abb 2 Einfluß verschieden langer Ohrpaßstücke mit gleichem Kanaldurchmesser auf den Schalldruckverlauf im künstlichen Ohr

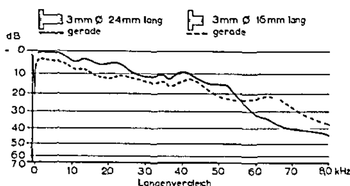


ABB 3 Einfluß verschieden langer Ohrpaßstücke mit gleichem relativ kleinem Kanaldurchmesser auf den Schalldruckverlauf im künstlichen Ohr

von Länge und Durchmesser (= doppelter Radius) des Bohrkanales im Ohrpaßstück in dem System Hörer, Ohrpaßstück und Gehörgang haben wir die von Guttner (1954) angegebene Formel umgestellt, die sich für den zu bestimmenden Widerstand in folgender Form ableitet:

$$W_D = \frac{l}{r^2}\, k \left[\frac{1}{r}\sqrt{2\mu\omega\varrho} + j\left(\omega\varrho + \frac{1}{r}\sqrt{2\mu\omega\varrho} - \frac{1}{l^2}\,\frac{\varrho c^2}{\omega}\right)\right],$$

W_D = Widerstand des Druckkammersystems, l = Länge der Bohrung, r = Radius der Bohrung, μ = Reibungskoeffizient, ω = Frequenz, ϱ = Dichte, c = Schallgeschwindigkeit $k = S/\pi$, S = abstrahlende Fläche Aus dem Faktor l/r^2, der vor dem übrigen Ausdruck steht, geht hervor, daß der Widerstand des Systems um so größer wird, je mehr die Länge zunimmt und um so kleiner, je größer der Radius wird Da in diesem Faktor der Radius in der 2 Potenz auftritt, ist zu schließen, daß der Einfluß des Radius wesentlich stärker ist als der der Länge In dem in Klammer stehenden Ausdruck wirken der Radius und die Länge in gleicher Richtung

In Abb 2 stellt die stark ausgezogene Kurve die Übertragungskennlinie des Systems Hörer, künstlicher Gehörgang und Kondensatormikrophon dar, wie sie sich ohne Einlagerung eines Ohrpaßstückes ergibt (Bei dieser und den nachfolgenden Abbildungen handelt es sich um die Wiedergabe von Originalregistrierungen, die Kurven wurden lediglich durch verschieden starke Überzeichnung kenntlich gemacht Da der Tonfrequenzanalysator (FTA BN 48302, R & S) mit linearer Frequenzteilung arbeitet, ist auch die Frequenzachse der Abb 2–7 linear geteilt (Hierdurch werden kleinere Unterschiede im oberen Tonbereich deutlicher dargestellt als bei logarithmischer Teilung!) Wird das Volumen des Gehörganges durch den Einsatz mit 6 mm Bohrung und 10 mm Länge von 2,5 cm³ auf 2 cm³ verringert, so entsteht die starke gestrichelte Linie, es kommt durch die Verkleinerung des Volumens wie erwartet zu einem Anstieg des Schalldruckes im Gehörgang, abgesehen von dem Bereich zwischen 4 und 5 kHz Bei weiterer Verringerung des Volumens *durch den Einsatz von 14 mm Länge bei gleicher Bohrung* auf 1,8 cm³ stellt sich der erzielte Druckanstieg in der dünn ausgezoge-

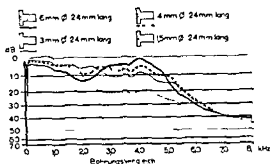


Abb. 4. Einfluß verschiedener Kanaldurchmesser bei Ohrpaßstücken gleicher Länge auf den Schalldruckverlauf im künstlichen Ohr

nen Kurve noch deutlicher dar. Verkleinert man das Volumen mit Hilfe des Einsatzes von 24 mm Länge und 6 mm Bohrung auf 1,3 cm³, so zeigt sich eine deutliche Schalldruckerhöhung im Frequenzgebiet unterhalb von 5 kHz von etwa 8 dB gegenüber der ersten Kurve. Der Anstieg im oberen Frequenzbereich, der sich bei den Volumen von 2 und 1,8 cm³ günstig bemerkbar macht, hebt sich hier wegen der erhöhten frequenzabhängigen Verluste in dem langen Bohrkanal wieder auf.

Die Abb. 3 stellt nochmals verschieden lange Ohrpaßstücke mit gleicher Bohrung gegenüber, um zu zeigen, daß auch bei engeren Bohrungen die bereits anhand der Abb. 2 beschriebenen Verhältnisse gelten. Dem langen Paßstück entspricht ein Gehörgangsvolumen von 0,8 cm³, dem kürzeren von 1,4 cm³. Dem kleineren Gehörgangsvolumen ist wieder eine geringe Schalldruckerhöhung unterhalb 5,5 kHz zugeordnet, dem größeren hingegen ein merklicher Gewinn von mehr als 10 dB oberhalb 6 kHz.

Den Einfluß verschiedener Bohrungsdurchmesser bei konstanter Länge zeigt Abb. 4. Hier wird deutlich, wie mit abnehmendem Radius (Bohrkanaldurchmesser) die Verluste im oberen Frequenzgebiet zunehmen, während im unteren Frequenzbereich ein dem Radius umgekehrt proportionaler Druckanstieg zu verzeichnen ist. Bei den Bohrungen mit 3 und

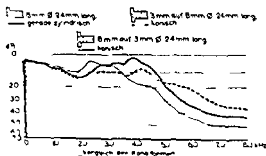


Abb. 5. Einfluß verschiedener Kanalformen bei konstantem Luftvolumen im künstlichen Ohr auf den Schalldruckverlauf

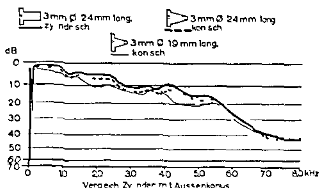


Abb. 6. Einfluß der äußeren Form des Ohrpaßstückes auf den Schalldruckverlauf im künstlichen Ohr

4 mm Durchmesser, die einem Gehörgangsvolumen von 0,8 und 0,9 cm³ entsprechen, halten sich die Gewinne unterhalb 2,5 kHz und die Verluste zwischen 2,5 und 5,0 kHz etwa die Waage, während bei der engsten Bohrung von 1,5 mm Durchmesser bei einem Volumen von 0,6 cm³ die Verluste zwischen 2,0 und 6,0 kHz, die fast 20 dB erreichen, weit im Vordergrund stehen. Der geringere Einfluß auf den Schallenergietransport, den eine Verkleinerung des Durchmessers von 6 mm auf 3 mm im Gegensatz zu einer weiteren Abnahme des Kanaldurchmessers auf 1,5 mm bewirkt, erinnert an die bekannte Tatsache, daß ein Gehörgang oft sehr weitgehend durch Ohrschmalz verengt sein darf, ohne daß es zu einer merklichen Höreinbuße kommt. Erst bei einer zusätzlichen geringen Verlegung, z. B. durch einen einzigen Wassertropfen, tritt plötzlich eine ausgeprägte Schwerhörigkeit auf.

Auf Grund der anatomischen Gegebenheiten wird es dem Hörgeräteakustiker meist nicht möglich sein, einen Kanal mit konstantem Durchmesser durch die ganze Länge des Ohrpaßstückes zu bohren. Meist zwingt die Form des Gehörganges die Bohrung an der einen Seite etwas enger zu gestalten oder veranlaßt, diese am Zapfenende, das zum Trommelfell hin zeigt, weiter zu formen. Wir dehnten daher unsere Modellversuche auf diese Fragestellung aus. In der Abb. 5 werden die Übertragungskurven verschiedener Kanalformen miteinander verglichen. Die stark ausgezogene Kurve gehört zum Paßstück mit der zylindrischen Bohrung von 6 mm Durchmesser bei einer Gesamtlänge von 24 mm, entsprechend einem verbleibenden Volumen im künstlichen Ohr von 1,3 cm³. Die starke gestrichelte Linie ist die Übertragungskurve eines trichterförmig gebohrten Ohrpaßstückes, wobei die engste Stelle mit 3 mm Durchmesser unmittelbar am Hörer sitzt, während der größte Bohrungsdurchmesser mit 8 mm gegenüber dem „Trommelfell", d. h. der Mikrophonmembran liegt. Das Gehörgangsvolumen beträgt ebenfalls 1,3 cm³. Die dritte Kurve, dünn ausgezogen, zeigt die akustischen Eigenschaften eines trichterförmig gebohrten Paßstückes, bei dem die engste Bohrung unmittelbar vor der Mikrophonmembran liegt und der weite Teil zum Hörer zeigt. Das Volumen von Bohr-

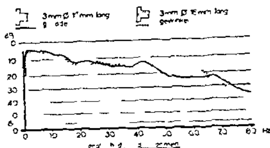


Abb. 7 Einfluß einer Knickung der Bohrung eines Ohrpaßstuckes auf den Schalldruckverlauf im künstlichen Ohr

kanal und Gehorgang beträgt wiederum 1,3 cm³ Hier kommt wohl sehr deutlich zum Ausdruck wie das zum Trommelfell hin weit geoffnete Paßstuck gegenuber dem gleichmaßig gebohrten die Übertragung der hohen Frequenzen fordert wahrend das mit der Trichterspitze zum Trommelfell zeigende Ohrpaßstuck eine obere Frequenzbegrenzung hervorruft Die Unterschiede zwischen den beiden Trichterformen betragen im hohen Frequenzgebiet teilweise mehr als 20 dB

Wollte man die Vorteile die eine Volumenverkleinerung des Gehorganges durch ein Ohrpaßstuck bringt so lange die Bohrung hinreichend weit gemacht werden kann nutzen so muß berucksichtigt werden daß das Kiefergelenk in den Gehorgang ragt und diesen beim Kauen abwechselnd erweitert und verengt Außerdem ist der Gehorgang in der Tiefe stark beruhrungsempfindlich des weiteren antwortet der Gehorgang auf eine standige Druckreizung mit einer verstarkten Absonderung von Ohrschmalz Das Ohrpaßstuck darf daher ab der Tiefe des Kiefergelenkes die Gehorgangswand nicht beruhren sondern muß einen gewissen Abstand von dieser einhalten Dieser praktischen Notwendigkeit tragt der folgende Versuch Rechnung In der Abb 6 sind 3 Ohrpaßstucke in ihren akustischen Eigenschaften gegenubergestellt Das Volumen im kunstlichen Ohr ist bei dem zylindrischen Einsatz auf 0,8 cm³ verringert bei dem konischen Paßstuck von 24 mm Lange auf 1 cm³ und bei dem kurzen konischen Ohrpaßstuck auf 1,5 cm³ reduziert Der Kurvenverlauf zeigt daß das zusatzliche Volumen zwischen der Oberflache des Zapfens und der Gehorgangswand die Ubertragungseigenschaften praktisch nicht beeinflußt Erst bei einer Verkurzung des gesamten Einsatzes auf 19 mm Lange treten merkliche Verluste auf Dieses Bild beweist daß eine begrenzte Verbesserung der Schallubertragung vom Horer zum Trommelfell durch ein uberlanges Ohrpaßstuck durchaus moglich ist Allerdings ist vorauszusetzen daß der Gehorgang genugend weit ist und eine ausreichend große Bohrung ermoglicht Andererseits sind bei engen Gehorgangen die hier aufgeworfenen Fragen ohne besondere Bedeutung da das Gehorgangsvolumen von Natur aus kleiner ist

Zuletzt soll die Frage beantwortet werden, ob die Knickung der Bohrung, wie sie entsprechend der Verwindung des natürlichen Gehörganges notwendig ist, einen Einfluß auf die akustischen Eigenschaften hat. In der Abb. 7 werden zwei Ohreinsätze von gleicher Länge mit gerader und gewinkelter Bohrung verglichen. Die Abweichungen der Übertragungskurven scheinen uns unerheblich, insbesondere, wenn man berücksichtigt, daß die gewinkelte Bohrung sowohl am Übergang vom Hörer zum Kanal als auch an dem Knick einen etwas größeren Querschnitt erhalten hat. Das Volumen im künstlichen Ohr betrug 1,4 cm³ für das Paßstück mit der geraden Bohrung und 1,6 cm³ für das mit der gewinkelten Bohrung.

SUMMARY

The transmission of the air conducted sounds from a hearing aid to the ear drum is very highly influenced by the exact incorporation of the ear mould itself. Besides this there are further remarkable facts causing loss of the transmitted sound energy particularly in the upper frequency range. These are (1) the size of the remaining air volume in the ear canal between the ear mould and the ear drum as far as its increase will reduce the transmitted sound pressure, (2) the frictional resistivity of the moving air molecules in the canal of the ear mould, (3) the length and form of the canal in the ear mould as a part of the sound conduction system.

In studies on an artificial ear concerning the relationship between length and form of the diameter of the canal in the ear mould it might be possible according to the form of the external ear canal to improve the effect of the sound transmission and the range of reception in the upper frequencies for approximately 10 db. The concave drilled ear canal form of the ear mould was found to be most advantageous when pointing with its largest diameter towards the ear drum.

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THE OTONEUROLOGICAL DIAGNOSIS OF INTRACRANIAL EXPANSIVE PROCESSES

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A total of 187 patients with a suspected intracranial expansive process were studied at the Otolaryngological Hospital University of Helsinki in co-operation with the Department of Neurosurgery. After a complete otoneurological and neurosurgical examination 126 of them were found to have an expansive process. The involvement could be neither excluded nor confirmed with certainty in 13 cases, and in 48 the possibility of an expansion was excluded completely. The material included 58 acoustic neurinomas, 52 of which were verified histologically. The otoneurological finding supported the diagnosis of acoustic neurinoma in 53 (91 per cent) cases. In the other cases of expansive processes of the posterior fossa 26 out of 39 (67 per cent) displayed symptoms suggestive of expansion of the posterior fossa. Otoneurological symptoms indicative of expansion were established in 8 (28 per cent) out of 29 cases with an expansive process external to the posterior fossa.

The role of the otologist in the diagnosis of tumours of the acoustic nerve is well known and generally acknowledged; expansive processes in the region of the posterior fossa are also known to come in general within the range of otoneurological diagnosis. On the other hand it is not always remembered that otological or otoneurological examination may elicit valuable additional information also when such a process is suspected elsewhere than in the posterior fossa. The otoneurological examination may give indications of the presence of the tumour and clinical examination may disclose further tumour tissue, e.g. in the patient's nose or nasopharynx, a specimen of which may be decisive for verification of the tumour.

The object of the present study was to ascertain how otoneurological examination may be helpful in the diagnosis of intracranial expansive processes. The authors desired especially to study the extent to which the usefulness of an otoneurological examination is dependent on the localisation of the process.

The material consisted of 187 cases which were distributed into four groups: I. Tumours of the acoustic nerve (acoustic neurinomas) 58 cases. II. Other expansive processes of the posterior fossa 39 cases. III. Intra-

cranial expansive processes outside the posterior fossa 29 cases IV Cases in which an intracranial expansive process was suspected but later excluded with certainty, 48 cases In addition 13 cases were included in which an expansive process was not diagnosed with certainty but had to be considered

The material which comprised 108 women and 79 men was examined in the five year period 1960–1964 at the Otolaryngological Hospital of the University of Helsinki in co operation with the Department of Neurosurgery The latter clinic also performed the neurological and neuroradiological examination of the patients and was responsible for all the operative therapy

METHOD OF EXAMINATION

A clinical ear nose and throat examination was first performed on all the patients *Audiological examination* (1) Pure tone audiometry was performed by audiometers calibrated by the NPI standard (2) In speech audiometry, speech threshold and maximal discrimination were determined (3) Recruitment was examined by the Fowler test (4) Adaptation was determined in some cases by the method published by Palva (1964) The threshold shift occurring in 3 min was measured The *vestibular examination* was performed by electronystagmography and the result was recorded by an ELEMA electrocardiograph equipped with a pre amplifier Before every examination the apparatus was calibrated by using flashing lights which were visible to the patient at an angle of 10 deg The caloric reaction was recorded while the patient was supine with his eyes closed in a dimly lit room Calorisation was performed by rinsing the patient s ears with water of 30° and 44°C for 30 sec Water containers with thermostats placed 1 m above the patient s head were used for the rinsing In addition to the caloric reaction spontaneous and positional nystagmus were also studied both by electronystagmography and by inspection A *porus roentgen examination* was performed on the persons who had not come from the Department of Neurosurgery If these examinations had already been made at the Department of Neurosurgery, they were usually not repeated in connection with the otoneurological examination The results obtained at both *the clinics in questions were combined in the final examination*

I ACOUSTIC NEURINOMAS

Acoustic neurinoma is a tumour which every otologist encounters sometimes For instance 8 7 per cent of the brain tumours reported by Cushing (1935) were acoustic neurinomas and the corresponding percentage in Olivecrona s (1927) material was 8 6 It is customary to speak of the classical otoneurological picture of acoustic neurinoma and indeed the disease picture caused by t

pattern is considered to cover e.g. impairment of hearing accompanied by a considerable discrepancy between the pure tone threshold and speech threshold, the latter being notably higher than the pure tone threshold would presuppose, the recruitment phenomenon is missing, Jerger's curve type III or IV predominates in Békésy audiometry, and according to many workers' opinion pathological adaptation also belongs to the picture. At vestibular examination, again, weak or abolished function is established as well as spontaneous nystagmus which is often of Bruns's type. Lately, however, increasing attention has been paid to the occurrence of cases in which the symptoms and examination results differ, and sometimes differ considerably, from this "classical" pattern. For instance House (1964) reported on the basis of 53 acoustic neurinomas operated on that the absence of the "classical" picture of acoustic neurinomas by no means excludes the possibility of its existence. The "classical" picture is encountered more often in connection with large than small acoustic neurinomas. The series published by House included 12 small and 41 large tumours. Twenty-two of the latter were "classical" audiologically and 19, nearly a half, differed in some way from this "classical" type. This may have been due in part to the old hearing defects of some patients.

Menzel *et al.* (1964) reported a case of acoustic neurinoma in which the audiological picture conformed fully to cochlear lesion: marked recruitment, small DL at the threshold level, small adaptation and Jerger's curve type II in Békésy audiometry. Audiological diagnosis is also hampered by the fact that the audiological picture may change with time. A case was reported by Jerger & Waller (1962) in which Békésy type I changed to type III within a year and discrimination decreased from 86 to 14 per cent. The vestibular examination is of great help also in the verification of acoustic neurinoma. According to House normal vestibular function argues very strongly against acoustic neurinoma. Forty-four of his patients complained of disturbances of equilibrium or vertigo, while 9 did not have these symptoms at all. Examination established vestibular disturbances in all of the patients, however, and consequently vestibular function was normal only in two.

Audiological studies which may be used in the examination of acoustic neurinoma include pure tone audiometry and speech audiometry, Békésy audiometry, determination of loudness *recruitment*, SISI and tone decay tests and determination of adaptation. Vestibular examination can be performed e.g. by means of ENG registration by which spontaneous nystagmus among other things can generally be established in an early phase. Spontaneous nystagmus is often manifested as Bruns's nystagmus which is small, rapid and regular to the healthy side and strong, slow and irregular to the affected side. The study of positional nystagmus is regarded as fairly important by Graf (19[illegible]2), although its occurrence in connection with acoustic neurinoma is still but little known. Spontaneous nystagmus to the side of the tumour is generally intensified in the final phase of the

TABLE 1 *Distribution of the material by age*

Age, years	Number	Age, years	Number
Under 21	3	41–50	22
21–30	5	51–60	20
31–40	3	61–70	5

tumour, and even vertical nystagmus may appear which is commonly regarded as a sign of a poor prognosis The function of the vestibular organ is best studied by the caloric test.

Acoustic neurinoma may emit symptoms not only via the acoustic nerve but also via other cerebral nerves The acoustic nerve and possibly also the facial nerve are mostly affected first, followed by cerebellar symptoms (Romberg's sign, ataxia, dysmetria, etc), general cerebral pressure symptoms and, finally, the possible pyramidal symptoms

Own Investigation Results

The material consisted of 58 cases of acoustic neurinoma, 52 of them verified histologically The remaining 6 cases were diagnosed with certainty although no operation was performed, either on account of the patient's high age or because of the small size of the tumour. There were 23 men and 35 women The patient's age at the time the tumour was diagnosed can be seen from Table 1

Almost exactly three-fourths (74 per cent) of the patients were 41–60 years of age The youngest patient was 11 years, and the diagnosis was verified histologically The oldest was 67 Forty-eight of the patients came for consultation from the Department of Neurosurgery, the remaining 10 came first to the Otolaryngological Hospital, from which they were sent after examination to the Department of Neurosurgery for treatment

Subjective symptoms

(1) The commonest symptom was impairment of hearing, which 57 patients complained of, only 1 patient had not noticed any deterioration of hearing (2) Forty-two patients complained of tinnitus which was thus not nearly as frequent a symptom as impaired hearing (3) Fifty-one patients had disturbances of equilibrium and vertigo, and for 39 of them locomotion in particular gradually became difficult Twelve complained of vertigo also at rest, 3 had had attacks of rotatory vertigo of Ménière's disease type (4) Three patients had difficulty in swallowing and 2 had hoarseness of long duration Eleven patients had had episodes of pain in the buccal region and 8 a rubbing sensation in the eye The time lapse from the onset of the symptoms was generally 1–10 years (47 cases) Three patients had had symptoms for less than 3 months, 3 for over 15 years

TABLE 2 *Result of pure tone audiometry*

Mean of hearing impairment at the frequencies 500 1000–2000 cps	Homo-lateral ear	Contra lateral ear
Under 16 dB	—	31
16–30 dB	3	15
31 60 dB	12	8
61 90 dB	10	4
Over 90 dB	20	—
Deaf	13	—
Total	58	58

General oto rhino laryngological examination

All the patients had dry ears at the time of examination. Fifty one had normal tympanic membranes, the other 7 patients had either dry tympanic membrane perforation or a cicatricial tympanic membrane as the sequela of otitis. Three patients had pharyngeal paresis and 2 had vocal cord paresis.

Audiological examination

The result of the pure tone audiometry is given in Table 2.

All the patients had sensorineural impairment of hearing in the homolateral ear; a small conductive component was associated with it in 2 patients. The impairment in the contralateral ear was conductive in 4 cases. It was possible to determine the speech threshold of the homolateral ear in 33 cases. 23 patients heard not a single word at speech audiometry, and the examination was impossible in 2 cases on account of disturbed powers of concentration and observation. Not a single patient had a normal speech threshold in the homolateral ear and only 3 of the 33 whose speech threshold could be measured achieved 100 per cent discrimination. The speech threshold of the contralateral ear was normal in only 9 cases, elevated in all the others. The Fowler test was possible in only 43 cases. It was negative for 40 patients, 2 had partial and 1 had complete recruitment.

Vestibular examination

Spontaneous nystagmus was established with inspection in 39 patients. It was of Bruns's type in 32 cases. With electronystagmography spontaneous nystagmus was established in 50 patients. The calorisation result can be seen from Table 3. It may be mentioned that the calorisation results were obtained by using water of 30° and 44°C, no stronger stimulation such as iced water was used.

TABLE 1 *Distribution of the material by age*

Age, years	Number	Age, years	Number
Under 21	3	41–50	22
21–30	5	51–60	20
31–40	3	61–70	5

tumour, and even vertical nystagmus may appear which is commonly regarded as a sign of a poor prognosis. The function of the vestibular organ is best studied by the caloric test.

Acoustic neurinoma may emit symptoms not only via the acoustic nerve but also via other cerebral nerves. The acoustic nerve and possibly also the facial nerve are mostly affected first, followed by cerebellar symptoms (Romberg's sign, ataxia, dysmetria, etc.), general cerebral pressure symptoms and, finally, the possible pyramidal symptoms.

Own Investigation Results

The material consisted of 58 cases of acoustic neurinoma, 52 of them verified histologically. The remaining 6 cases were diagnosed with certainty although no operation was performed, either on account of the patient's high age or because of the small size of the tumour. There were 23 men and 35 women. The patient's age at the time the tumour was diagnosed can be seen from Table 1.

Almost exactly three-fourths (74 per cent) of the patients were 41–60 years of age. The youngest patient was 11 years, and the diagnosis was verified histologically. The oldest was 67. Forty-eight of the patients came for consultation from the Department of Neurosurgery, the remaining 10 came first to the Otolaryngological Hospital, from which they were sent after examination to the Department of Neurosurgery for treatment.

Subjective symptoms

(1) The commonest symptom was impairment of hearing, which 57 patients complained of, only 1 patient had not noticed any deterioration of hearing. (2) Forty-two patients complained of tinnitus which was thus not nearly as frequent a symptom as impaired hearing. (3) Fifty-one patients had disturbances of equilibrium and vertigo, and for 39 of them locomotion in particular gradually became difficult. Twelve complained of vertigo also at rest, 3 had had attacks of rotatory vertigo of Menière's disease type. (4) Three patients had difficulty in swallowing and 2 had hoarseness of long duration. Eleven patients had had episodes of pain in the buccal region and 8 a rubbing sensation in the eye. The time lapse from the onset of the symptoms was generally 1–10 years (47 cases). Three patients had had symptoms for less than 3 months, 3 for over 15 years.

TABLE 2 *Result of pure tone audiometry*

Mean of hearing impairment at the frequencies 500–1000–2000 cps	Homo-lateral ear	Contra lateral ear
Under 16 dB	—	31
16–30 dB	3	15
31–60 dB	12	8
61–90 dB	10	4
Over 90 dB	20	—
Deaf	13	—
Total	58	58

General oto-rhino-laryngological examination

All the patients had dry ears at the time of examination. Fifty one had normal tympanic membranes, the other 7 patients had either dry tympanic membrane perforation or a cicatricial tympanic membrane as the sequela of otitis. Three patients had pharyngeal paresis and 2 had vocal cord paresis.

Audiological examination

The result of the pure tone audiometry is given in Table 2.

All the patients had sensorineural impairment of hearing in the homolateral ear, a small conductive component was associated with it in 2 patients. The impairment in the contralateral ear was conductive in 4 cases. It was possible to determine the speech threshold of the homolateral ear in 33 cases. 23 patients heard not a single word at speech audiometry and the examination was impossible in 2 cases on account of disturbed powers of concentration and observation. Not a single patient had a normal speech threshold in the homolateral ear and only 3 of the 33 whose speech threshold could be measured achieved 100 per cent discrimination. The speech threshold of the contralateral ear was normal in only 9 cases, elevated in all the others. The Fowler test was possible in only 43 cases. It was negative for 40 patients, 2 had partial and 1 had complete recruitment.

Vestibular examination

Spontaneous nystagmus was established with inspection in 39 patients. It was of Bruns's type in 12 cases. With electronystagmography, spontaneous nystagmus was established in 50 patients. The calorisation result can be seen from Table 3. It may be mentioned that the calorisation results were attained by using water of 30° and 44°C, no stronger stimulation such as iced water was used.

TABLE 3 *Result of the calorisation test*

	Number of cases	
	Homo lateral ear	Contra lateral ear
Normal reaction	1	22
Hypoexcitability	18	36
No response	39	—
Total	58	58

Other cerebral nerves and the cerebellum

The symptoms caused by the cerebellum and other cerebral nerves are shown in Table 4

Roentgenography of the porus

Data on roentgenography of the porus were available in 56 cases, this information was not available in 2 instances Porus roentgenography was normal for 4, the finding was suspect for 5, and in the remaining 47 cases roentgenography definitely suggested acoustic neurinoma

Otoneurological diagnosis

Fifty-five of the cases were patients on whom one or other of the authors had performed an otoneurological examination There were thus only 3 cases in which the diagnostic evaluation had been made by somebody else On the strength of the otoneurological examination, acoustic neurinoma was regarded as certain in 53 cases (91 per cent) and as probable but not completely verified in 2 cases A diagnosis of cerebellopontine angle tumour was regarded as certain in 3 cases, in 2 of them the possibility of acoustic neurinoma was also considered, but in the third case another tumour of the posterior fossa than acoustic neurinoma was found to be involved

TABLE 4 *Other cerebral nerve and cerebellar symptoms*

Symptom	Number
Facial paresis or paralysis	37
Disturbance of corneal sensitivity	34
Disturbance of buccal touch sensation	30
Paralysis of the abducens	4
Velar paralysis	3
Vocal cord paralysis	2
Cerebellar symptoms	36

Operative therapy

Fifty two patients were operated on and the tumour was verified histologically in all these cases. Total extirpation was performed in 44 cases, subtotal in 7 cases and exploration only in 1 case. Eight (16 per cent) of the operated patients died.

Discussion

The material supports the often repeated statement that cases of acoustic neurinoma display many deviations from the so called classical disease pattern. The course may be reminiscent of Meniere's disease with manifest acute episodes of vertigo, the hearing deficiency may be very slight or completely absent, complete recruitment may appear, etc. In the present series 3 patients had attacks of vertigo exactly like those of Meniere's disease. The corresponding incidence in House's roughly equally large series was 5. The mean of the pure tone threshold was over 15 dB for all the patients at the frequencies 500, 1000, 2000 cps. The hearing impairment was so slight in 2 patients, however, that their pure tone threshold ranged from 15 to 20 dB. Twenty three patients failed to hear a single word in speech audiometry. It was possible to determine the pure tone threshold but not the speech threshold for 12 of them. The speech threshold of 1 patient was 36 dB but the speech discrimination was nevertheless 0. Discrepancy between hearing of pure tones and hearing of speech is in fact an important symptom suggestive of acoustic neurinoma. The absence of recruitment was a fairly distinct symptom; however, complete recruitment was established in 1 and partial recruitment in 2 cases. According to House positive recruitment in acoustic neurinoma may be due to the tumour pressing on the internal auditory artery rather than on the nerve itself, perhaps giving the hearing defect the picture of a cochlear lesion. Hearing defects were encountered in 91 per cent of the material reported by Dix & Hallpike (1950) and recruitment was present in 5 of the 90 cases. It was contended also by Pfalz (1964) that positive recruitment does not rule out the possibility of acoustic neurinoma and that its diagnosis is never fully certain by mere audiological examinations. The calorisation result was a fairly reliable indication of acoustic neurinoma also in the present material. Vertigo and disturbances of equilibrium were encountered as subjective symptoms in 51 patients (88 per cent) but examination revealed vestibular lesion in 57 (98 per cent). These figures concur well with the results reported by House, viz. 83 and 96 per cent.

The otoneurological diagnosis as a whole was fairly reliable: acoustic neurinoma was regarded as definite in 53 cases (91 per cent), as possible but not proven in 4 cases; in only one case was it concluded from the otoneurological examination that the involvement was not an acoustic neurinoma. In 6 cases the neurosurgical finding was that acoustic neurinoma was not certain: the disease picture had developed very rapidly in 1 case, hardly any symptoms were established in 2 patients and 3 had a

syndrome which did not concur with the clinical picture of acoustic neurinoma. In 5 of these cases the otoneurological diagnosis was acoustic neurinoma and only in 1 was another process considered to be involved. As evidence of the fact that the diagnosis of acoustic neurinoma is not always easy, may be mentioned that destruction of the labyrinth had been performed on 2 patients of the material some time before the examination to relieve the attacks of vertigo.

In addition to the definite cases mentioned above, the material included 6 patients for whom it was not possible either to exclude acoustic neurinoma with certainty or to confirm it convincingly even after the otoneurological and neurosurgical examination. In 3 cases the finding of the otoneurological examination was that the condition involved was not acoustic neurinoma; in the other 3 cases it could neither be established nor ruled out with certainty.

Case report

A boy, aged 11. Hearing in the left ear deteriorated rapidly 1 ½ years before the patient came for an examination, and a year later there were increasingly serious episodes of disturbed equilibrium. Otoscopy revealed nothing abnormal in the patient's ears. The left ear was deaf at pure tone audiometry; discrimination was 0 at speech audiometry. Bruns's nystagmus was present. The left ear did not respond to the caloric test; the reaction of the right ear was practically normal. Tactile sensation of the left cheek and the corneal reflex were distinctly reduced. Dysmetria, dysdiadochokinesia and ataxia were present. Operation revealed a tumour extending from the pontine angle to the edge of the foramen magnum. The histological diagnosis was acoustic neurinoma. The boy made a good recovery and was discharged.

II. OTHER EXPANSIVE PROCESSES OF THE POSTERIOR FOSSA

Although acoustic neurinoma is the expansive intracranial process for which otoneurological diagnosis generally gives the best results, this examination is fairly important and provides valuable information also in many other expansive diseases of the posterior fossa. According to Dix and Hallpike (1950) otoneurological symptoms are always overshadowed by neurological symptoms when the acoustic nerve is not involved primarily in the process. It may nevertheless be rather difficult, sometimes impossible even, to distinguish some tumours of the posterior fossa from acoustic neurinoma by otoneurological examination alone. For instance, the picture produced by a meningioma in the posterior fossa often resembles fairly closely that of acoustic neurinoma and there is no finding which would differentiate reliably and clearly between these two conditions. Several symptoms have however been mentioned as significant for this differential diagnosis. In acoustic neurinoma the hearing is affected in an earlier phase and the hearing defect progresses more rapidly. A hearing defect caused by meningioma has, according to House (1964), a purer picture

of a lesion of the acoustic nerve in which cochlear symptoms are missing, poor discrimination compared with the pure tone threshold, absent recruitment and Bekesy's audiogram type III or IV. Bearing in mind how much the above audiological symptoms vary even in acoustic neurinoma it can be understood that they cannot lend very great support in differential diagnosis. Many investigators are of the opinion that roentgenography is in fact the most reliable diagnostic aid. In addition, meningioma is sometimes calcified and thus easier to distinguish from acoustic neurinoma. Cases have also been reported in which the same patient has had both acoustic neurinoma and meningioma. Nager (1964) published 3 such cases.

Own Investigation Results

The material consisted of 11 meningiomas, 9 spongioblastomas, 2 hemangioblastomas, 4 cholesteatomas and 8 other tumours. The histologically verified cases thus totalled 34. The material also comprised 5 definite cases of expansion of the posterior fossa which were not verified histologically. Exactly two thirds (26) were women and one third (13) men. Nine patients were under 20, the youngest 6 (not verified), 10 and 11 (both had spongioblastomas). All but 2 of the rest were 31–60 years of age. Thirty four patients came for the otoneurological examination from the Department of Neurosurgery, the remaining 5 came first to the Otolaryngological Hospital from which they were referred to the Department of Neurosurgery because of the examination finding.

Subjective symptoms

Ten patients attended for examination less than 6 months after the onset of the symptoms, 12 6–12 months and the remaining 17 1–10 years after the onset. One half (20) of the patients complained of poor hearing, 17 of tinnitus in one ear, 22 of difficulty in walking and 10 of vertigo. Three of the last mentioned had had episodes of rotatory vertigo. In addition 2 patients had speech disorder and 2 dysphagia.

General oto-rhino-laryngological examination

All the patients had dry ears, 3 revealed an after-condition of otitis, and nothing pathological was found otoscopically in the other patients. Two patients had vocal cord and 2 velar paralysis.

Audiological examination

Pure tone audiometry showed that 16 patients had normal hearing in the homolateral ear, 9 had a hearing threshold of 16–60 dB and 7 of over 60 dB but nevertheless measurable. The hearing threshold in 7 cases could not be measured at all. The contralateral ear had normal hearing in 31 cases, the *remainder* had a hearing threshold ranging from 16 to 45 dB. The hearing defect of 5 patients was purely conductive, of the others per

ceptive A normal speech threshold was established in 13 (exactly one-third) patients, it was elevated in the remainder of which 9 had discrimination 0 The Fowler test was performed in 32 cases and was negative in every one

Vestibular examination

Spontaneous nystagmus was established with inspection in 21 persons Electronystagmography, however, showed spontaneous nystagmus in a total of 28 patients Spontaneous nystagmus was distinctly to the side of the lesion in 9 cases, directed to the contralateral side in 19 Calorisation showed that the reaction of the ear on the homolateral side was normal in 12 cases, 16 patients had hypoexcitability, and no response at all was elicited in 11 cases The reaction was normal on the contralateral side in 20 cases, 18 patients had hypoexcitability, and no response was elicited in 1 case

Other cerebral nerves and the cerebellum

Facial paresis was present in 19 cases, disturbances of buccal tactile sensation in 16 and disturbance of corneal sensibility in 14 cases Cerebellar symptoms were established in 28 cases

Otoneurological diagnosis

The finding was that 26 patients had a definite expansive process in the posterior fossa It was not possible in 7 cases to be certain of the diagnosis, but the finding suggested an expansive process in the region of the posterior fossa The otoneurological finding for 6 patients was normal and consequently warranted no diagnostic hypotheses

Operative therapy

Total extirpation was possible in 27 cases, subtotal extirpation was performed in 5 cases and exploration only in 2 cases

Discussion

The study showed that the diagnostic benefit of the otoneurological examination is not confined to cases of acoustic neurinoma It also provides valuable diagnostic data in other expansive processes of the posterior fossa No decisive differences from acoustic neurinoma were established by the audiological and vestibular examinations from, say, meningiomas of the posterior fossa This group also displayed fairly serious hearing defects, pure tone audiometry revealed that the other ear of 7 patients was completely deaf, and for another 7 the hearing threshold was above 60 dB Nine patients had no discrimination in speech audiometry, it was possible to determine the pure tone threshold of 2 of them Discrepancy between hearing of pure tones and of speech was also demonstrated Although 16 patients had a normal pure tone threshold in the ear on the side of

the lesion only 6 of them had 100 per cent discrimination Not a single case of meningioma of the posterior fossa displayed recruitment or even partial recruitment but partial recruitment was established in 2 acoustic neurinoma patients and complete in 1 This supports in its own small way House s statement that the audiological picture of meningioma of the posterior fossa lacks the cochlear features which are occasionally encountered in connection with acoustic neurinoma The origin of the tumour is fairly important for otoneurological diagnosis In all the 14 cases where the pontine angle was the site of origin a typical pontine angle syndrome was elicited by otoneurological examination On the other hand pathological symptoms other than spontaneous nystagmus were established by otoneurological examination only in roughly half of the cerebellar processes

In addition to the cases described above the material included 7 cases in which symptoms suggestive of an expansive process of the posterior fossa were present but the diagnosis could not be confirmed The otoneurological finding was perfectly normal for 2 of them for 5 patients it suggested an expansive process in the region of the posterior fossa

III EXPANSIVE PROCESSES OUTSIDE THE POSTERIOR FOSSA

Twenty nine patients 5 of them children with an expansive intracranial process outside the posterior fossa were studied All the cases involved a histologically verified intracranial tumour In 1 case symptoms suggestive of intracranial tumour were established first in the Otolaryngological Hospital while the others came for examination to this Hospital from the Department of Neurosurgery The clinical examination revealed tumour tissue in the middle ear in 1 case and in the nasal meatus in 2 cases In one of the two latter cases polyps had been removed from the same meatus a couple of months earlier

Subjective symptoms

Four patients complained of poor hearing and tinnitus in one ear 7 had disturbances of locomotion and 2 had vertigo one of them as ambiguous attacks Three patients had dysphagia and 1 patient had persistent hoarseness

Audiological examination

The hearing was perfectly normal at pure tone audiometry in 21 patients, lowered in 8 Two of these 8 patients had unilateral deafness 4 had a unilateral partial perceptive hearing impairment and in 2 the hearing defect was conductive The speech threshold was normal in 16 patients and elevated in the other cases They included 2 cases in which discrimination was 0 Recruitment was absent in all 4 patients with a perceptive hearing defect

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Vestibular examination

Spontaneous nystagmus was established with inspection in 2 cases and with electronystagmography in 4 patients. The result of the caloric test was normal in 19 cases, there was hypoexcitability in 6 and no response in 4 cases.

Other cerebral nerves and the cerebellum

Five patients had facial paralysis, 3 had trigeminus symptoms, 3 had pharyngeal paralysis, 1 patient had vocal cord paralysis and 2 had cerebellar symptoms.

Otoneurological diagnosis

Nothing suggestive of an expansive intracranial process was seen in 21 cases; in 8 cases the finding supported this diagnosis, and actual tumour tissue was seen in 3 of them and the tumour could be verified histologically from the sample taken.

Discussion

Although the finding of the otoneurological and otological examination is usually negative for tumours external to the posterior fossa, otological consultation is often also indicated. The tumour may emit otoneurological symptoms which are reflected as functional disturbances without tumour tissue itself being found, or the direct destructive effect of a tumour may extend to the region of the ear, nose, epipharynx and pharynx and then can often be verified histologically.

IV. CASES OF SUSPECTED TUMOUR WHICH PROVED NEGATIVE ON EXAMINATION

The material also comprised 48 cases sent from the Department of Neurology for examination for a suspected intracranial expansive process which could definitely be ruled out on the basis of the examinations made. Twenty seven of the patients had normal hearing, 8 had a partial perceptive and 7 a conductive hearing impairment, and 6 had complete unilateral deafness. The result of the vestibular examination was normal for 26 patients, the reaction was weak or abolished in 22 cases. Otoneurological examination established in 5 of the patients examined symptoms which might have tallied with an intracranial expansive process, but 43 displayed nothing indicative of one.

CONCLUSIONS

The result of the examination can best be presented in tabular form (Table 5). The finding was not, of course, the same in all the cases in which the possibility of an intracranial expansive process was indicated.

TABLE 5 *Result of the otoneurological examination*

	Number	Positive	Uncertain	Negative
Acoustic neurinoma	58	53	4	1
Other expansive processes of the posterior fossa	39	26	7	6
Tumours outside the posterior fossa	29	8	—	21
Suspected tumours excluded at examination	48	2	3	43

by the otoneurological examination i e in the cases in which the finding was regarded as positive On the contrary it varied according to the case however so that the diagnosis of expansion was considered certain In 53 out of 58 cases (91 per cent) the diagnosis of acoustic neurinoma was considered certain on the strength of the otoneurological examination in 4 uncertain There was only 1 case in which the finding argued clearly against acoustic neurinoma This patient was a woman of 37 who had had for a year a sensation of numbness in her left cheek for 4 months difficulties of equilibrium and headache she suspected that the hearing in her left ear had deteriorated slightly there was no tinnitus The pure tone threshold of the left ear was 28 dB the speech threshold was elevated correspondingly maximal discrimination being 90 per cent The Fowler test was negative There was weak ambiguous spontaneous nystagmus to the right Calorisation gave a practically normal reaction for both ears In several cases in which the otoneurological finding indicated acoustic neurinoma the finding was not classical

In 26 of the 39 (67 per cent) cases of expansive processes of the posterior fossa the otoneurological finding distinctly suggested involvement while nothing abnormal was demonstrated in 6 patients The otoneurological finding substantiated this in all the 14 cases in which the expansive process had its origin in the cerebellopontine angle In contrast half of the processes deriving from the cerebellum were cases in which the finding was completely normal or spontaneous nystagmus was the only finding Symptoms suggestive of an intracranial expansive process were established in 8 out of the 29 cases (28 per cent) of an expansive process outside the posterior fossa In 2 of these patients tumour tissue was demonstrated in the nasal meatus and in 1 patient in the middle ear and these tumours could be verified histologically

Symptoms regarded as signs of expansion were established on otoneurological examination in 2 of the 48 cases in which an expansive process was first suspected but later ruled out convincingly by examination Typical trigeminal neuralgia was finally diagnosed in one of these 2 cases who had concomitant ear symptoms In the other case basal meningitis was demonstrated in the posterior fossa

ZUSAMMENFASSUNG

An der Universitäts-Ohrenklinik des Zentralkrankenhauses von Helsinki wurden in Zusammenarbeit mit der neurochirurgischen Klinik 187 Patienten wegen Verdachts eines expansiven, intrakraniellen Prozesses untersucht. Das Ergebnis der Untersuchung zeigte, dass bei 126 Patienten ein expansiver Prozess mit Sicherheit anzunehmen war, bei 13 Patienten ein derartiger Prozess bezweifelt werden musste und in 48 Fällen die Möglichkeit des Vorliegens eines expansiven Prozesses ausgeschlossen werden konnte.

Das Material enthält 58 Akustikusneurinome. Bei 53 Fällen (91 %) hat die otoneurologische Untersuchung die Diagnose der Akustikusneurinome gestützt. Von anderen expansiven Prozessen der hinteren Schädelgrube (39 Fälle) zeigten 26 (67 %) Symptome, die mit Sicherheit auf einen expansiven Process hinwiesen. Ein expansiver Prozess ausserhalb der hinteren Schädelgrube lag bei 29 Patienten vor, wobei 8 (28 %) von diesen otoneurologische Symptome zeigten, die auf eine Expansion hinwiesen.

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A STUDY OF THE EFFECTS OF AUDITORY STIMULI ON RESPIRATION

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The purpose of the investigation was basically to determine whether or not respiration would be altered by the perception of auditory stimuli. The experimental conditions dealt with intensity of the stimulus, validity of the technique as compared to voluntary thresholds, and test-retest reliability.

The findings indicated first that there is a significant slowing in the respiration cycle during tonal stimulation as compared to the respiration cycle in the absence of tonal stimulation; that slowing of the respiration cycle is greater for low intensity tonal stimulation than for tonal stimulation of high intensity; that respiration thresholds agree well with voluntary thresholds determined by the conventional method; and that there is good agreement between test-retest respiration thresholds.

These findings support the previous experimental and clinical observations of Rousey, and indicate that additional research should be pursued on children and subjects with various types of pathological entities.

It is emphasized that proper measurement of the respiration cycle is of critical importance to insure success with the method.

INTRODUCTION

The necessity for an early determination of hearing sensitivity is particularly pertinent in the diagnosis of language disorders in young children. Unless a hearing loss has been ruled out it is frequently not clear whether loss of hearing sensitivity or a neurological problem is the primary reason for a language disorder.

As the current indirect methods of assessing auditory sensitivity are not without drawbacks in all situations, then it follows that we must seek either to improve on the present techniques or else to discover new methods for diagnosis. With new techniques we should be able either to obtain the same information as with the old, only more adequately, or else supplement the information already obtained.

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A recent investigation by Rousey, Snyder & Rousey (1964) stimulated the following study which was carried out with the above concept in mind. It was postulated that perhaps a new indirect test could be devised either to supplement information gained from present indirect techniques, or else to gain information in situations where results from the present techniques were obscure or inadequate.

Furthermore, it was felt that the techniques should be relatively free of such disturbing factors as electrode placement and the use of electric shock in conditioning. Another reason pertained to the need for exploring other physiological functions aside from EEG and EDR as possible means of obtaining information relative to the threshold of tonal perception.

To this end it was decided to investigate the effects upon breathing, if any, of the perception of tonal stimuli. It was felt that if the regular rhythmic act of breathing is disturbed by the introduction of an auditory stimulus, and if this possible disturbance in breathing could be easily measured, then we might have access to a more functional indirect tool for hearing measurement.

A method for recording respiration described by Ackner (1956) was considered to be adequate for measuring the rate of breathing. It was also judged to be uninvolved enough so that it would not be particularly frightening to children, or cumbersome to administer. Hence, if the method could be successfully adapted to the testing of hearing, it might prove to be more functional and efficient than the present indirect testing techniques.

In lieu of the previous discussion then, the primary questions to be investigated in this study were: (1) Is there a significant change in the duration of the breathing cycle as a function of tonal stimulation over combined levels and for specific levels? (2) Does greater slowing of the breathing cycle occur for low tonal presentation levels as compared to high tonal presentation levels? (3) Is there agreement, within specified limits, between threshold as obtained by standard audiometry and thresholds determined by the respiratory test? (4) Is there test-retest agreement for auditory thresholds obtained by slowing of the breathing cycle as a result of tonal stimuli?

MATERIAL AND METHODS

Thirty-six subjects were used for this study. The subjects reported no prior histories of decreased hearing or otologic involvement in the ear under test. The subjects consisted of a group of males and females between the ages of 18 and 30 years. One ear of each subject was selected for study. Hence the results of 36 ears are presented.

Each ear of each subject was tested by standard audiometry. The better ear was then selected for study. If no difference in sensitivity existed be-

tween ears then the right ear was chosen with the first subject, the left ear with the second subject the right ear with the third subject etc

The tone stimulus was generated by an Otarion audiometer, Model 1000 This audiometer equipped with TDH 39 earphones mounted in MX/41 AR ear cushions was checked for frequency and intensity The stimulus frequency was 1990 Hz as measured by a Beckman Frequency Counter Model 52308 The actual sound pressure levels of the tonal stimuli used in the experiment as measured on an Allison artificial ear Model 3A were 69, 37 28 19 and 12 decibels The duration of the stimulus was approximately 3 seconds

All tests were conducted in a double wall Industrial Acoustics Corporation sound proof room (Model 1200) The subjects were asked to lie in a reclining position on a cot placed in the sound suite Prior to this a mercury in rubber strain gauge was fastened around the upper body at the xiphoid process after the procedure as described by Rousey *et al* (1964) With the subject in a comfortable reclining position the experimenter positioned the headset Only one earphone of this headset was connected to the audiometer The other earphone acted as a dummy for positioning

The mercury in rubber strain gauge mentioned previously was attached to the carrier amplifier of a four channel Sanborn recorder Model 67 1200 For the purposes of this study only one channel of the recorder was utilized The connection between the strain gauge and the recorder was accomplished with a basic Wheatstone type bridge The circuitry utilized for this bridge arrangement and exact resistance and capacitance values are described by Ackner (1956)

This equipment combination appeared to adequately pick up and record the subject s respiratory cycle The record trace was thought to be a reliable representation of the subject s respiratory cycle with regard to the specific aspect considered in this study e g rate or duration

The experimenter was situated in a room outside and adjacent to the sound proof room occupied by the subject out of visual contact With the exception of a one way amplification system to transmit the standard audiometry *responses of* the subject there was no auditory communication between experimenter and subject This was an intentional arrangement to eliminate as nearly as possible any stimuli outside the subject s immediate environment which could have an affect upon the measured respiratory rate

Situated thus the experimenter had unlimited access and freedom of movement to monitor the Sanborn recorder and operate the pure tone audiometer Another operation for which the experimenter was responsible was the simultaneous depression of the marker switch on the recorder with the presentation of the tonal stimulus from the audiometer The results of this operation increased the accuracy of analyzing the record of the subject This was so because the black mark left on the recording

paper from the above procedure showed the viewer exactly where the tone-stimuli or simulated stimuli had been presented in relation to the respiratory trace Several methods have been suggested for the simultaneous activation of the test stimuli and the recorder marker However, the one chosen here utilized a single-pole, single throw, push button type switch, secured in a small cardboard box Attached to the switch was enough insulated wire to allow it to be connected to the marker assembly on the recorder, and then to be placed on the floor close to the audiometer The switch could then be controlled with the foot of the experimenter

For the purposes of this study, the above procedure allowed for sufficient proximity, relative to time, of initiation of the two functions, i e, presentation of the test stimuli and activation of the marker switch

After placing the headset on the subject, as mentioned above, the door to the sound suite was closed and a one-way communication system turned on allowing the experimenter to hear the standard audiometry responses of the subject Standard audiometric pure tone thresholds were obtained at 1990 Hz An ascending technique for determining threshold, described by Carhart & Jerger (1959) was followed The subject responded by saying yes each time the tone was heard

After obtaining the standard audiometric threshold, the strain gauge was fastened around the upper body of the subject as previously described He was then informed that it would no longer be necessary for him to respond to the tonal presentations, and that he should just lie quietly Each subject was also cautioned not to make any gross movements which would interfere with the belt around his stomach Subjects were also told how long they would be in the room, which was approximately twenty-five minutes

Before the testing sequence to be described below was initiated, each subject was allowed to lie quietly for three to four minutes The first minute or so of this three-to-four minute rest period was utilized by the experimenter to balance or match the resistance imposed on the strain-gauge around the stomach of the subject with the electrical outflow of the recorder apparatus This procedure was carried out with a 1000 ohm variable-resistor placed between the strain-gauge and the recorder apparatus The remaining portion of this 3–4 minute period was spent with the door to the sound suite closed and with the subject lying quietly In this manner the subject was allowed a brief adjustment period

Test and retest conditions were repeated for all 36 subjects using the procedure to be described subsequently After each subject had completed the first test sequence, which lasted approximately 25 minutes, he was allowed a period of one-half hour in which he could leave the testing suite and participate in any activity he desired Following this one half hour "break" the subject re-entered the sound suite and the complete testing procedure was repeated, with the exception of re-determining the pure tone threshold at 1990 Hz by standard audiometry It was felt that the deter-

TABLE 1. *Order of presentations of tones and simulated test events re SPL*

True = Tone on   False = Simulated tone

1	23 dB True	31	12 dB True
2	69 dB False	32	12 dB False
3	28 dB True	33	23 dB False
4	37 dB False	34	28 dB True
5	28 dB False	35	28 dB True
6	19 dB True	36	69 dB False
7	19 dB False	37	12 dB True
8	28 dB True	38	23 dB False
9	28 dB True	39	12 dB False
10	23 dB True	40	37 dB False
11	37 dB True	41	19 dB False
12	37 dB True	42	12 dB False
13	19 dB True	43	19 dB True
14	69 dB True	44	19 dB True
15	69 dB False	45	69 dB False
16	69 dB True	46	69 dB True
17	23 dB True	47	12 dB True
18	23 dB False	48	69 dB False
19	12 dB True	49	28 dB False
20	69 dB True	50	28 dB False
21	28 dB False	51	12 dB True
22	23 dB False	52	19 dB False
23	37 dB True	53	69 dB True
24	23 dB True	54	12 dB False
25	23 dB True	55	37 dB True
26	37 dB False	56	28 dB False
27	37 dB False	57	19 dB False
28	23 dB False	58	19 dB True
29	19 dB False	59	37 dB False
30	37 dB True	60	12 dB False

mination of threshold one hour prior would suffice for retest as well as for the test situation. The retest situation also lasted 25 minutes.

The above procedure was followed for all subjects except three. The change involved here was that these subjects received the retest sequence one day later because of prior commitments, rather than after the usual one half hour "break".

Each subject was presented a total of sixty test events. Each event had a temporal duration of approximately three seconds. The order of presentation of the test events is shown in Table 1. The sequence, as presented, was determined by writing one of each of the stimulus or simulated events on a 3" by 5" index card and shuffling them thoroughly for 20 minutes. When this task was completed it was assumed that the stack of sixty cards, each card containing one of the sixty test events, was in a random order. This then was the order selected both for test and retest conditions.

The test frequency, 1000 Hz, was presented at six different Sound Pres-

sure Levels, i e, 69 dB, 37 dB, 28 dB, 23 dB, 19 dB and 12 dB Each SPL was presented to the subject five times, and for each actual stimulus presentation there was a simulated or false event With ten stimuli presentations (five actual and five simulated) at six levels of intensity for one frequency, each subject received a total of sixty stimulus events, thirty of which were actual tonal presentations and thirty of which were simulated presentations

RESULTS

The breathing cycles which occurred during the presentations of the thirty stimulus events and the thirty simulated events were measured The measurements were accomplished with a clear plastic ruler using the millimeter scale The criteria used for selecting the cycle to be measured was to start the initial point of measurement at the nearest peak or valley to the onset of the tone The black mark placed on the chart at the onset of a tone or simulated event allowed the scorer to rapidly and accurately locate the appropriate breathing cycle Depending upon which of the two points, peak or valley, was closer to the onset of the tone, the next peak or valley was taken for the final point of measurement Hence, a straight line measurement was taken of each complete breathing cycle occurring during the stimulus events and simulated events

At each of the six SPL's presented in this study each subject had then five numerical values representing the length of the breathing cycle which occurred during the presentation of that tone For each subject there were also thirty numerical values representing the length of the breathing cycle occurring when the marker switch on the recorder was depressed alone, without an accompanying tonal stimulus For purposes of comparison, these simulated events were also recorded by levels This same procedure was followed also for each subject in the retest condition

After the raw score data had been recorded in the above manner the five stimulus values for each SPL were ranked in a descending order and the median value was computed A similar procedure was utilized in computing the median for the thirty values constituting the simulated events as they related to duration of breathing cycles A difference score was obtained then between the stimulus value and the simulated value at each SPL Positive numbers indicated greater slowing of breathing during the presentation of an auditory stimuli Conversely, negative numbers indicated that the simulated values were longer in duration than tonal stimulation

Statistical treatment of the above data utilized the McNemar test (Siegel, 1952) for the significance of changes This test provided for treatment of tone-on versus tone off conditions over combined intensity levels, and over individual intensity levels When all levels combined were submitted to the above noted statistical test, χ^2 values of 75 3 and 71 0 were obtained for the test and retest respectively Both values were found to be significant beyond the 0 001 level of confidence

TABLE 2 *Comparison of tone on versus tone off at each sound pressure level*

Intensity levels (SPL)	Test χ^2	Retest χ^2
12 dB	20 48[b]	18 58[b]
19 dB	30 25[b]	12 03[b]
23 dB	17 46[b]	25 71[b]
28 dB	7 50[a]	1 75
37 dB	4 00[a]	9 33[a]
69 dB	4 36[a]	5 63[a]

[a] Statistically significant beyond the 0 05 level
[b] Statistically significant beyond the 0 001 level

With reference to the analysis of the data at each sound pressure level, it may be seen in Table 2 that at all sound pressure levels in the test condition, and at five of the six sound pressure levels in the retest condition, there were statistically significant slowings of the breathing cycles during tonal stimulation as compared to the breathing cycles during simulated events These findings indicate, therefore, that there is a significant slowing in the duration of the breathing cycle during tonal stimulation

As a next step in the treatment of the data, the tonal presentation levels were arbitrarily dichotomized into low and high All tonal presentation levels at 23 dB and below, i e, 12 dB, 19 dB and 23 dB, were designated as low, all tonal presentation levels 28 dB and above, i e, 28 dB, 37 dB and 69 dB, were designated as high The decibel level at which the greatest slowing in the breathing cycle occurred during tonal stimulation as compared to the simulated event was then determined for each subject

To test the significance of the frequency of greatest slowing between low and high dB levels in the test and retest conditions, The Binomial Test was employed Z scores of 4 83 and 4 5 were obtained for the test and retest, respectively These values are significant at the 0 001 level of confidence and indicate, that the greatest slowing in breathing during tonal stimulation as compared to the breathing cycle when no tonal stimulus was present, occurred at the low intensity presentation levels

These results were anticipated, since, as will be observed by a re-examination of Table 2 the levels of significance tend to increase (higher level of confidence) as tonal intensity is decreased both in the test and retest conditions It would appear, therefore, that low intensity tones induce a stronger focusing of attention in the subject as compared to high tones

It will be recalled that voluntary thresholds had been obtained on the subjects as the initial step in the study Therefore, it was decided to test the agreement of respiratory to voluntary thresholds for the test and retest conditions Respiratory thresholds in this context refers to the decibel level at which the greatest slowing in the breathing cycle had occurred

during tonal stimulation. For the purpose of this comparison agreement between tests was arbitrarily defined as thresholds which did not differ by more than 15 decibels. The results of this analysis using the Binomial Test indicated that both the test and retest respiration thresholds agreed significantly (0.001 level) with the voluntary thresholds within the limits as defined in this experiment.

Further analysis of the data involved the significance of agreement between respiratory thresholds in the test situation and respiratory thresholds in the retest situation. In carrying out this analysis, thresholds were arbitrarily considered to be in agreement if they did not differ by more than 10 dB. Treatment to determine the significance of agreement between test and retest thresholds utilized The Binomial Test. This analysis revealed significance of agreement beyond the 0.001 level of confidence.

The importance of the technique used in measuring the breathing cycle accompanying tonal stimulation should be stressed. A method choosing the nearest peak or valley *after* the onset of the tone was considered originally in this investigation, as well as one which chose the *exact* point on the wave which corresponded to the onset of the tone. Both the above techniques proved either ineffectual in terms of the information sought, or cumbersome to administer. The method presented in the text appears to be a key factor for success with the respiratory technique. To reiterate, the method of measurement used in this investigation chose as the initial point of measurement, the peak or valley closest to the onset of the tone, regardless of whether or not the chosen peak or valley occurred before or after the onset of the tone. The distinguishing feature between the method used, and the two others mentioned previously, is that in the method chosen the initial point of measurement did not necessarily correspond to the exact onset of the tone, nor did it have to occur after the onset of the tone, but that it could actually occur *before* the presentation of the tone. The important consideration was that the point (peak or valley) chosen for measurement be the *closest* peak or valley in relation to the onset of the tone.

DISCUSSION

The first question posed in the introduction concerned change in the rate of breathing between instances when an auditory pure tone was being presented, and simulated instances of equal time duration when no tone was being presented. The comparisons were first between the total number of tonal presentations and the total number of simulated tonal events both in the test and retest condition, and second, between the tonal stimulations and simulated events as each specific sound pressure level. The χ^2 values obtained when comparing the tone-on values with the tone-off values afforded an affirmative answer. Specifically, a significant change in breathing was observed at a 0.001 level of confidence when tone on values were

compared with tone off values over combined levels of intensity The same findings of a statistically significant slowing with the tone on versus the tone off maintained for the individual sound pressure levels with the exception of the 28 dB level in the retest situation The fact that in eleven of the twelve comparisons a significant slowing was found under tonal stimulation supports the clinical observations of Rousey

With reference to question two, which pertained to the comparative effectiveness of low and high level tonal stimuli to elicit slowing changes in the breathing cycles, it was demonstrated that the low level stimuli were significantly more effective in producing change In short what appears to be a focusing of attention to perceive low level tones results in a prolongation of the breathing cycle This finding of greater slowing in breathing at low intensity levels would seem to imply that an ascending method of threshold searching would be preferred in the clinical application of the technique

Question three was associated with the agreement in auditory thresholds between the respiration and the conventional methods It was clear from the findings that the two methods give essentially the same threshold within the limits of the present experiment

The final question which was posed pertained to the test retest agreement of the respiration thresholds The findings indicated that highly significant agreement exists

It is concluded therefore that the method merits further investigation as a possible additional tool for clinical use It has the definite advantage of being innocuous both for children and adults as demonstrated by Rousey and does not require elaborate preparation of subjects

ZUSAMMENFASSUNG

Der eigentliche Zweck dieser Untersuchung war festzustellen ob das Atmen durch das Wahrnehmen von auditorischen Reizen geändert wird Die Untersuchung befasste sich mit der Intensität des Reizes der Gultigkeit der Technik mit selbstbestimmten Schwellen verglichen und der Zuverlässigkeit der Versuche

Die Ergebnisse der Untersuchung zeigten zuerst dass der Atmungszyklus bedeutend verlangsamt wird während des Tonreizes verglichen mit dem Atmungszyklus bei Abwesenheit des Tonreizes Das Verlangsamen des Atmungszyklus ist bedeutender während niedriger Intensität des Tonreizes als während höherer Intensität Die Atmungschwellen stimmen mit den selbstbestimmten Schwellen gut überein und Atmungsschwellen in wiederholten Versuchen stimmen gut miteinander überein

Diese Ergebnisse unterstutzen Rouseys frühere Versuche und klinische Beobachtungen und zeigen dass weitere Untersuchungen an Kindern und Versuchspersonen mit verschiedenen pathologischen Zuständen notwendig sind

Es wird betont dass das richtige Messen des Atmungszyklus von grosser Wichtigkeit ist um mit der besprochenen Methode Erfolg zu erzielen

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THE ACTION OF HORMONES ON JUVENILE NASOPHARYNGEAL ANGIOFIBROMA

A Case Report

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A case of juvenile nasopharyngeal angiofibroma treated preoperatively first with androgen and then with estrogen is reported. Under androgen therapy the tumor appeared to enlarge somewhat. This was followed by a course of estrogen therapy which resulted in a prompt and dramatic involution and decrease in size of the tumor. It became very firm and permitted evulsion with a minimal (600 cc) blood loss for this type of tumor. The response of this tumor to estrogen was similar to that found by one of the authors in four previously unreported cases. Microscopic pictures showed a dramatic fibrosis with maturation of the vascular and connective tissue elements. Preoperative estrogen therapy is recommended as a supplement but not a substitute for surgery. The blood loss is definitely decreased.

INTRODUCTION

Whenever any tumor exhibits distinct sexual dimorphism the endocrine system is obviously implicated. The juvenile nasopharyngeal angiofibroma (JNF) is apparently such a tumor. As has been reported in several large series, Barnwalter (1930), Figi (1940, 1950), Martin, Ehrlich & Abels (1948), Hubbard (1958), Harma (1959) and Sternberg (1954), this disease is almost exclusively found in the adolescent male. The rare cases reported in the female leave reasonable doubt as to the microscopic and clinical diagnosis which appears to be confirmed by Figi's report from the Mayo Clinic showing a 7.9% incidence in females in the first twenty years and 0% in the last ten years of the cases reviewed.

Pathogenesis

In 1959 Schiff presented a composite theory of pathogenesis for the JNF which implicated the fibrovascular elements of tissue under endocrine stimulation. In this manner it was possible to explain the location and sexual dimorphism of such a tumor. He postulated that there was an

overactivity of the pituitary gonadotrophins which resulted in a relative hypogonadal state. Estrogens were used to inhibit the gonadotrophins as well as to increase and mature the fibrous connective tissue of this tumor. The latter findings were demonstrated microscopically. De Judicibus (1961) substantiated the role of gonadotrophins by finding an increased excretion in the urine of these patients. Further confirmation of the effect of estrogens on the isolated fibroblast was recently presented by Ozzello (1964), which also helped explain the fibromatogenic effect of estrogen as shown earlier by Lipschutz (1950).

Pathology

The tumor arises at the age of from 10 to 30 years and originates from the rhinopharynx of the posterior part of the nose, from where it spreads by expansive growth to the surrounding structures, to which it locally adheres and which it can destruct by pressure necrosis. In the third decade the growth-energy of the tumor decreases, but no total spontaneous remission has ever been observed for the single reason that it has always been necessary to treat the patient. However, it is clear that the inclination to recurrence decreases as the patient grows older.

The tumor consists of a smooth or lobulated firm mass. It is harder than a choanalpolyp and is harder in older than in younger patients. In young patients it is mainly reddish and in older whitish. The surface is often ulcerated if it has been exposed to traumata or secondary inflammation.

Histopathology

The JNF has no proper capsule but is covered by an epithelium corresponding to its location. It is an angiomatous collagen connective tissue with vessels of every appearance. Many of them, especially in young patients and especially towards the surface of the tumor, have a wall which only consists of a single or two layers of endothelial cells. There is a marked endothelial proliferation. Often you find clusters of a few endothelial cells with no lumen between them. The connective tissue is loose and both the endothelial cells and the fibroblasts have a very immature appearance. In older patients the vessels are fewer and bigger with a more mature endothelial bounding and the connective tissue is more dense and mature with abundant collagen fibrils and spindle-shaped fibroblasts.

Symptomatology

The first symptom of the disease is stenosis of one or both sides of the nose. Later there are recidivating and often violent nosebleeds. The eustachian tubes and lachrymal canals can be closed, involving respectively reduced hearing and tear discharge. In more advanced cases there can be infiltration of the nasal sinuses and orbitae, but seldom of the skull. Sometimes you see destruction and deformation of the nasal and facial skeleton.

Therapy

Even if the tumor is not malignant properly speaking and thus does not metastasise treatment is indispensable because of its expansive growth and the increasing tendency to epistaxis.

Operative removal is generally considered to be the right treatment. It is well known that a very strong bleeding commonly appears from the vascular tumor during its extirpation. Even after preoperative or preoperative ligation of one or both external carotids there is often a very violent bleeding. Some authors even dissuade from biopsy because this can cause much bleeding too. Treatment with electrocoagulation as a rule also brings about a great bleeding. To prevent bleeding different preoperative courses of proceeding have been recommended.

X-ray treatment undoubtedly reduces the vascularity of the tumor but has to be reserved for patients over 18 years old, as it in younger patients stops the growth of the facial skeleton too early. In larger doses the treatment can lead to serious complications owing to necrosis of the tissue around the tumor. It is difficult to place radium needles in the tumor. The needles are often dislocated and cause strong bleeding. Erich (1955) therefore recommends radon seeds of 1 mc placed at a distance of 1 1/2 to 2 cm apart in the tumor.

Martin (1948) noticed that the JNF mainly occurs in patients who are sexually underdeveloped. On the basis of this observation and because the tumor has a tendency to remission at the same time as full sexual maturity is obtained he supposed that the formation of the tumor was due to reduced androgen production. He therefore gave testosterone preoperatively and found that the growth of the tumor came to a standstill and that the tendency to bleeding decreased. Martin's observations are confirmed by Delarue *et al* (1956) who also found a histologic maturing of the tumor. Erich (1955), Gignoux, Tokizawa & Gaillard (1959), Reynaud, Khan & Kahn (1955) and Sternberg (1954) have at the most noticed a decreased tendency to bleeding.

One of us (Schiff 1959) reported earlier 2 cases of JNF treated with androgen and 2 other cases treated with estrogen. He found a far greater effect of the estrogen treatment both on the size of the tumor, the maturing of its tissue and decrease in tendency to bleeding. Both androgens and estrogens inhibit the activity of the pituitary gland but estrogens have by far a stronger effect. Estrogens furthermore have a direct effect on the connective tissue and bloodvessels. The fact that the JNF is not found in females in addition supports the expectation of a greater effect of estrogen than androgen therapy.

As preoperative hormone therapy in cases of JNF has not been reported in Scandinavian literature we shall report the following case in which such therapy has been used.



Fig. 1. Carotid angiography showing the JNA before treatment.

Case Report

The patient is an 11 year old boy who is admitted under the diagnosis tumor rhinopharyngis dxt. He has previously been essentially healthy. The year before admission he gradually developed a total stenosis of the right side of the nose and a partial stenosis of the left side of the nose. At the same time he has had repeated nosebleeds.

The boy is a little more developed than would correspond to his age. There are no dysendocrine characteristics and he is in good general condition.

At indirect rhinopharyngoscopy there seems to be a tumor in the rhinopharynx, for this reason the rhinopharynx is examined under general anaesthesia by application of a soft palate retractor. It appears that there is a gray reddish lumpy tumor, which practically fills up the whole rhinopharynx with a broad basis originating from the posterior and right wall. At touch it easily bleeds. It feels firmer than a choanal polyp.



Fig. 2 A. Section of the JNF before treatment × 120

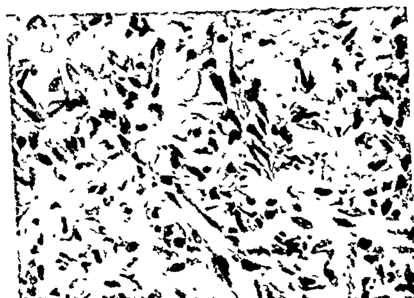


Fig. 2 B. Section of the JNF before treatment × 445

X-ray examination of the nasal sinuses showed diffuse shadows of the sinuses. By repeated antral punctures blobs of pus are evacuated from both maxillary sinuses.

X-ray examination with tomography of the rhinopharynx showed a shadow in the right side of the *rhinopharynx* with extension into the right choana which is extended. There seems to be destruction of the medial lamina of the pterygoid process.

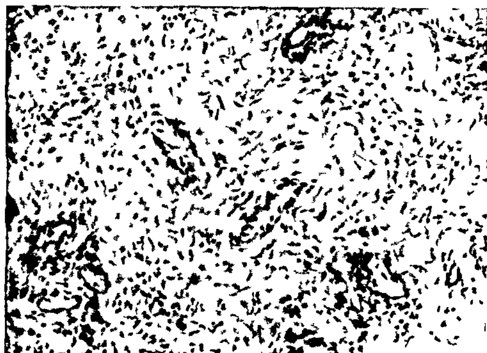


Fig. 3. Section of the JNF after treatment. ×120

Carotid angiography on both sides showed a vascular tumor in the right side of the rhinopharynx (Fig. 1). The vessels form an irregular network with blood supply from a thick arteria maxillaris interna dxt. There is no blood supply from the left side.

Under general anaesthesia using a soft palate retractor a biopsy was taken. At this there was moderate bleeding. The tissue was full of small and large vessels with much proliferating immature endothelium. Most of the vessel walls consist of only one layer of endothelium and scattered in the tissue are islets of 2 or 3 endothelial cells without any lumen between them. The vessels are lying in a loose connective tissue with immature fibroblasts with rounded nuclei (Fig. 2 A and B).

As a preoperative treatment the patient got 25 mg of testosterone a day for 6 weeks. Repeated rhinopharyngoscopy showed that the tumor seemed to grow larger. A new carotid angiography showed that it actually had grown.

In connection with the angiography the patient however got a hemipareses on the left side of the body. Further treatment of the tumor therefore had to be interrupted until the neurological symptoms disappeared.

Two months later hormone therapy was started again. We gave 5 mg of stilbestrol 3 times a day for 4 weeks. During this treatment the size of the tumor decreased unmistakably. Its consistency got harder and its color grew more whitish. The passage of air improved and there was no more bleeding. The patient could now smell again.

The tumor was removed under general anaesthesia. It was now so small that it was impossible to place a snare around it easily. *It therefore had to be loosened* from the medial lamina of the right pterygoid process. An incision was made in the posterior wall of the rhinopharynx down to the prevertebral fascia. A Peters snare was placed around the base of the tumor from the right nostril

and a firm and steady pull outward was applied to the snare while the tumor was loosened from the posterior wall and the roof of the rhinopharynx with an elevator through the oral cavity. The walnut size tumor was evulsed and drawn out through the right nostril. *During the operation blood loss was a* small as 600 cc. even though time was taken to demonstrate the method of the operation. The bleeding stopped after electrocoagulation and the application of a postnasal tampon which was removed after 48 hours. There was no postoperative bleeding.

Microscopy of the tumor showed that the connective tissue now was considerably increased and dense compared to the biopsy before treatment. It is now closely packed with collagen fibrils and mature fibroblasts. The mastcells are increased in number and content and there is marked metachromasia reflecting an active formation of mucopolysaccharides. The vessels are now mostly of intermediate size. Their endothelium is more normal. The endothelial cell clusters have disappeared (Fig. 3).

DISCUSSION

This case is suitable for drawing the attention to preoperative hormone therapy of patients with JNF.

Furthermore, there is good reason to notice the value of angiography of the external carotids in these vascular tumors, as has been demonstrated earlier by Huber (1960). In this case the angiographies have given a good representation of the tumor's size and localization and they gave the information that the tumor received its blood supply *from the right side* only. This fact could have been of importance if it had been necessary to ligate the external carotid because of violent bleeding.

In connection with the operation there was in this case only moderate bleeding (600 cc) in proportion to the often perilous bleedings which may occur at operative removal of juvenile angiofibromas. There is reason to believe *that this is* a consequence of the hormone therapy. One of us (Schiff 1959) has had the same experience in 6 other cases. In the last 3 which were operated with the same technique as used in this case bleeding was less than 500 cc.

The tissue of the tumor was much more mature both considering its angiomatous and its fibrous part after hormone therapy than before. This alteration could hardly have happened spontaneously. We have given first testosterone in one period and then estrogen in another. A biopsy after the end of the androgen therapy would of course have been interesting, but we could *not* expose the patient to the bleeding risk *of one* more biopsy. Judging from the macroscopic alterations we incline to the opinion that the estrogen therapy was decisive. This opinion is supported by the angiographies which showed *that the tumor had grown* during therapy with testosterone.

In short we have the impression from the course of this case that estrogen therapy produced a considerable *maturing* of the tumor tissue and with it the reduced tendency for operative bleeding.

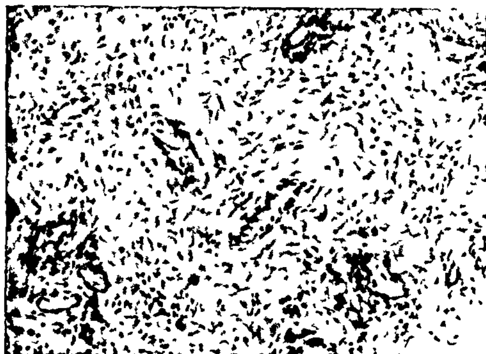


Fig. 3. Section of the JNF after treatment. ×120.

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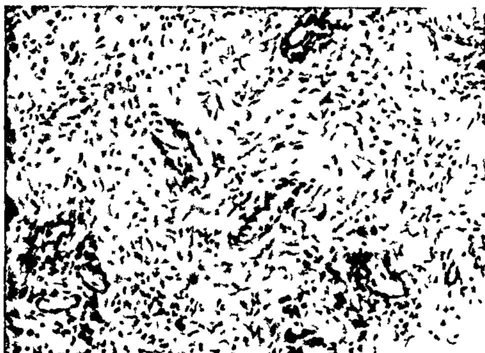


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STUDIES ON PROGRESSIVE HEREDITARY PERCEPTIVE DEAFNESS IN A FAMILY OF 335 MEMBERS

II Characteristic Pattern of Hearing Deterioration

E H Huizing A H van Bolhuis and D W Odenthal
Leiden The Netherlands

From the Department of Otolaryngology (Head Prof Dr H A E van Dishoeck), University of Leiden

Analysis of the sweep frequency audiograms of the 58 affected members tested revealed a characteristic pattern of progression of hearing deterioration in the family under observation Five stages of impairment viz A E and their intermediate phases could be distinguished It was observed that at first only the high frequencies above about 1000 Hz deteriorate This occurs in two phases first up to 60 dB and then up to 80 dB Thereafter hearing in the low frequency region deteriorates similarly while the high tone loss remains almost constant It is suggested that this separate and successive impairment of high and low frequency hearing might be explained by the existence of a high and a low frequency system in the cochlea as recently established in various investigations The two step progression of hearing loss could be explained by the difference in excitability between outer and inner hair cells as observed experimentally It is assumed that the outer haircells degenerate first resulting in a 60 dB loss and that thereafter the inner haircells become involved causing about 80 dB hearing loss

Part I of this study dealt with the genetic and general audiological results of our investigations into progressive hereditary perceptive deafness in a family of 335 members In the present part the characteristic pattern of hearing deterioration as found in this family will be treated

An attempt is made to explain this characteristic pattern of the progression of hearing loss from recent physiological anatomical and biochemical data on the cochlea

Analysis of the Audiometric Pattern of Progression of Hearing Loss

Analysis of the pure tone sweep frequency audiograms of the 58 affected members tested revealed that the progression of the hearing deterioration in the family investigated follows a distinct pattern Several stages of hearing impairment (correlated with age) can be distinguished as the progression from normal hearing to severe deafness comes to a relative

ZUSAMMENFASSUNG

Es wird über einen Fall von Nasenrachenfibrom berichtet, der präoperativ erst mit Androgen und dann mit Östrogen behandelt wurde. Während der Androgenbehandlung vergrösserte sich der Tumor etwas. Er wurde dann mit Östrogen behandelt, was eine prompte und deutliche Involution und Verminderung des Tumors mit sich führte. Der Tumor wurde sehr fest und liess sich mit einem für diesen Tumortyp minimalen Blutverlust entfernen. Die Reaktion dieses Tumors auf Östrogen war gleich der, die von einem der Verfasser in vier früheren Fällen gefunden wurde, über die jedoch bisher nicht berichtet worden ist. Mikroskopisch zeigte sich eine ausgeprägte Fibrose mit reifgewordenen Blutgefässen und Bindegewebe. Präoperative Östrogenbehandlung wird ergänzend empfohlen, aber nicht als Ersatz für eine Operation. Der Blutverlust wird definitiv vermindert.

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STUDIES ON PROGRESSIVE HEREDITARY PERCEPTIVE DEAFNESS IN A FAMILY OF 335 MEMBERS

II. *Characteristic Pattern of Hearing Deterioration*

F. H. Huizing, A. H. van Bolhuis and D. W. Odenthal
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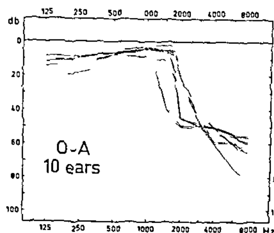


Fig. 1

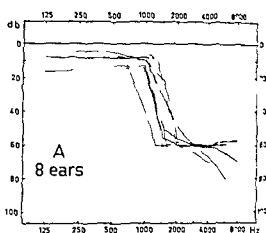


Fig. 2

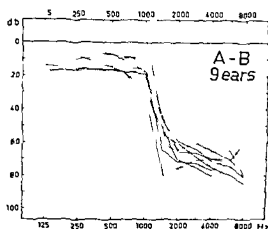


Fig. 3

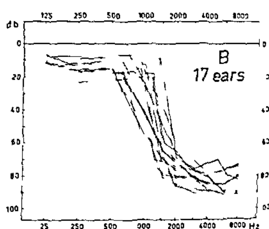


Fig. 4

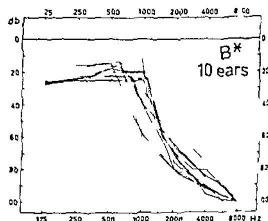


Fig. 5

Figs. 1–5. Stages of hearing impairment A and B (B*) and intermediate phases 0–A and A–B. (See text.)

arrestation" (slowing down of deterioration) a few times. Six typical stages were differentiated, stage 0 representing normal hearing, stage E the most severe hearing loss found, while stages A, B, C and D represent intermediate phases.

First in early childhood the hearing loss starts as an impairment in the high frequency range, beginning at the end of the tone scale. This high

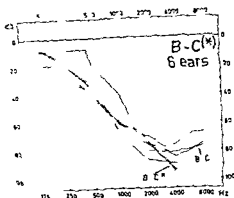


Fig 6

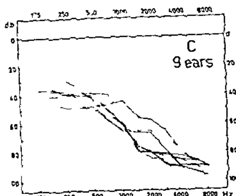


Fig 7

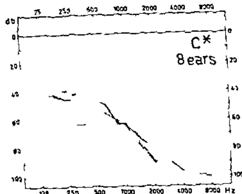


Fig 8

Figs 6–8 Stage of hearing impairment C and C* and intermediate phase B–C (See text.)

tone loss increases rapidly with age and is characterized by a gradual extension of the impairment to lower frequencies (0 A cases, Fig 1) The progression seems to come to a temporary halt when the impairment has reached a threshold loss of about 60 dB and covers the frequency region above circa 1000 Hz This stage is called *stage A* (Fig 2) and is characterized by normal hearing up to 1000 Hz, followed by a steep fall in the audiometrical curve of about 80 dB per octave to a hearing loss of about 60 dB for frequencies above 2000 Hz

With further progression the hearing below 1000 Hz still remains unaffected whereas the hearing loss for the high frequencies gradually increases from 60 dB to about 80 dB (A B cases Fig 3)

The second "relative arrestation" then occurs and is called *stage B* (Fig 4). It is characterized by normal hearing below 1000 Hz, and 80 dB loss for all frequencies beyond 2000 Hz The steepness of the fall of the curve has increased to about 100 dB per octave

With increasing age the low frequency region now becomes impaired whereas the high tone loss remains at the 80 dB level (B C cases, Fig 6)

Stage C (Fig 7) is the third stage of "relative arrestation" and is characterized by a 40–50 dB low frequency loss, and an 80 dB impairment in the

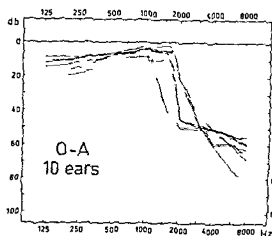


Fig 1

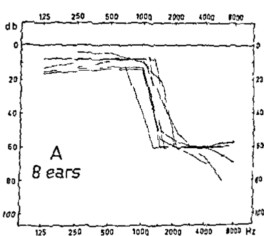


Fig 2

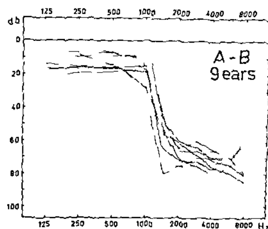


Fig 3

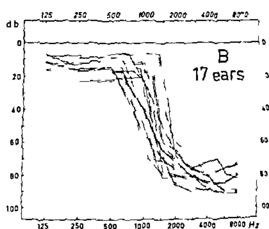


Fig. 4

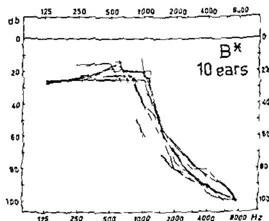


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First, in early childhood, the hearing loss starts as an impairment in the high frequency range, beginning at the end of the tone scale. This high

In a number of cases the high tone loss was not consistent at the 80 dB level throughout all high frequencies, but showed a gradual increase beyond about 3000 Hz whereas the pattern of the progression *per se* was completely identical in all other respects These audiograms are named according to the general stage of degeneration to which they belong and are marked by an asterisk B*, B*–C*, C*, C*–D* and D* (Figs. 5, 6, 8, 9 and 11)

DISCUSSION

In the audiometric pattern of the progression of deafness demonstrated in Figs 1–14, two important features are worth noting

1 A completely separate deterioration of the hearing for the high frequencies (above about 1000 Hz) and for the low frequencies At first only the high tones become affected up to a loss of about 80 dB, whereafter the low tones gradually become impaired

2 The threshold loss increases in steps At first the hearing impairment proceeds rapidly to a level of about 60 dB, and then to about 80 dB This progression in two stages is most marked in the deterioration in the high frequency area, but is also present when the low frequency region is affected

Both observations may be explained by some recently established physiological cytological and biochemical data on the cochlea

1 *Separate deterioration of high and low frequency hearing*

Recent investigations on monkeys of Katsuki, Suga & Kanno (1962) indicate that on account of differences in the frequency response curves, two systems in the cochlea can be distinguished one for low frequencies, the other for high frequencies A distinction between a high and low frequency region in the cochlea was also observed by Smith & Sjöstrand (1961), when by means of electron microscopic studies they found a difference between the nerve endings of the external haircells of the basal turn and those of the upper turn Neurobiochemical studies on guinea pigs by Wersall, Hilding & Lundquist (1961) also point this way In the basal turn of the cochlea these authors found cholinesterase activity in all rows of outer haircells in the apical turn, however, in the inner row only

Odenthal (1963) demonstrated that in man a distinct difference exists between the neural representation of tones below some 1000 Hz and those of the higher frequency region This neural representation was found to be similar to that in cats, guinea pigs and monkeys

The separate deterioration of the high and low frequency hearing observed in the progressive perceptive deafness in the members of the family of the present study, might be explained by the experimentally established existence of two systems in the cochlea Since these two systems seem to

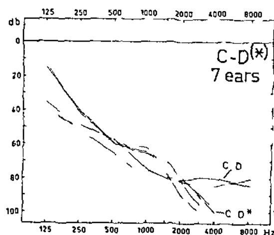


Fig 9

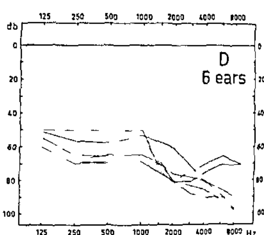


Fig 10

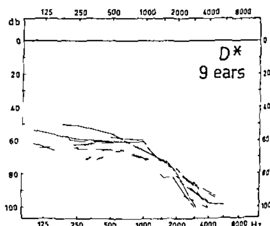


Fig 11

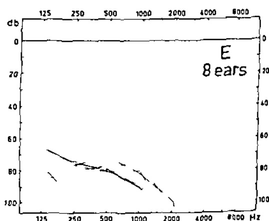


Fig 12

Figs 9–12 Stages of hearing impairment D, (D*) and E and intermediate phase C D* (See text)

high frequencies The low tone loss now progresses from 40 dB to some 60 dB, while the high tone loss still stays at the 80 dB level (C D cases, Fig 9) After this *stage D* (Fig 10) is attained

Stage E (Fig 12) is the most severe stage of hearing impairment measured This stage of almost complete deafness was only observed in members over 45 years of age

darauf hingewiesen, dass diese zeitlich getrennte Degeneration der hohen und der niedrigen Frequenzen mit der Existenz eines Systemes in der Cochlea für die hohen Töne und eines anderen für die niedrigen Töne im Zusammenhang stehen könnte. Die zweiphasige Progression des Hörverlustes wäre aus einer Erregungsdifferenz zwischen den inneren und äusseren Haarzellen zu erklären. Es wird angenommen, dass zuerst die äusseren Haarzellen degenerieren, was einen Verlust von 60 dB verursacht, und dass in zweiter Linie die inneren Haarzellen zugrunde gehen mit der Folge eines Verlustes von 80 dB.

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overlap only to a small extent a degeneration of one of them may lead to a fairly circumscribed hearing loss. This is in accordance with the sharp fall in the audiograms at stage A and B. From our clinical evidence, the boundary between the low and high frequency system in humans seems to be situated at 1000–1500 Hz.

2. *Two-step increase of hearing loss*

The two-step increase of hearing loss, first to 60 dB then to 80 dB may be explained by experimentally established differences between the outer and inner haircells. As has been found in various investigations, a difference in excitability exists between the outer and inner haircells (Tasaki 1954, *Katsuki, 1962, Rosenbluth, 1962*). *In order to get a response*, a 40–60 dB greater stimulus is required for the inner haircells than is necessary for the outer haircells (Katsuki, 1962).

CONCLUSION

From the analysis of the pattern of progression of the perceptive hearing loss as measured by means of sweep frequency audiometry, and the correlation of its results with recent findings on cochlear function, the following *pattern of degeneration might be assumed for the progressive perceptive* deafness in the family of the present study.

1. In the beginning, the outer haircells in the high frequency system degenerate, resulting in about 60 dB threshold loss for all frequencies above about 1500 Hz. As the low frequency area remains unaffected an abrupt fall in the audiogram results at the boundary between the high and low frequency regions, i.e. at about 1000–1500 Hz (stage A).
2. The inner haircells of the high frequency system next become involved. This produces an increase of the high tone loss to 80 dB, and a still more abrupt transition from the low to the high frequency part of the audiogram (stage B).
3. With the next step the low frequency system begins to degenerate in its outer haircells (stage C).
4. Eventually the inner haircells of the low frequency system become involved, and a more or less *flat* hearing remnant remains (stage D and E).

ZUSAMMENFASSUNG

Aus den *kontinuierlichen (sweep frequency) Audiogrammen von 58* untersuchten schwerhörigen Mitgliedern einer Familie ergibt sich eine typische Form der Progression von Schwerhörigkeit. Fünf charakteristische Stadien, A–E, sind zu unterscheiden. Zu Beginn nimmt das Hören von Tönen mit einer Frequenz über 1000 Hz ab. Dies geschieht in zwei Phasen: erst bis 60 dB und dann bis 80 dB. Später *fängt auch ein ebenfalls zweiphasiger* Rückgang der niedrigen Frequenzen an, während der Verlust für die hohen Töne gleichbleibt. Es wird

tegration in the central nervous system in order to carry out the necessary coordination between head and body movement. It is known that severe disturbances of body equilibrium occur following bilateral ablation of the dorsal roots of C1, C2 and C3 in cats (Magnus & Storm van Leeuwen 1914) and monkeys (Cohen 1961).

In a survey of the literature we found only three investigations concerning this somatic sensory and vestibular integration upon single neurons, all performed on cats. Pompeiano & Cotti (1959) found convergence of exteroceptive and proprioceptive somatosensory afferents and vestibular afferents in Deiters' nucleus without reference to neck receptor afferents. Dumont (1960 and 1964) noted convergence of vestibular impulses and impulses arising from radial nerve stimulation. Kornhuber & Aschoff (1964) found convergence of vestibular and deep somatic afferents in the motor cortex.

The purpose of this investigation was to more thoroughly explore vestibular somatic convergence and interaction in a limited area of the vestibular nucleus, including the medial and descending nuclei with special regard to the influence of neck receptor afferents, the relative influence of the different sensory modalities and the role played by the cerebellum in somatic sensory influences.

MATERIAL AND METHODS

The electrical activity of vestibular neurons from 19 cats was recorded utilizing a six-cathode ray oscillograph.

Preoperatively the animals were observed for their posture in static positions and their ability to perform skillful movements. Only those animals which performed normally were used.

The preliminary operations were carried out under ether anaesthesia. These consisted of tracheotomy, placement of a femoral vein catheter, bilateral round window silver ball electrode implantation (performed with the aid of a Zeiss microscope) and exposure of the left occipital cortex and cerebellum. In order to expose that portion of the cerebellum through which the microelectrodes were to be stereotaxically passed, a portion of the left bony tentorium was carefully excised with small bone cutting instruments.

Fifteen of the animals were immobilized for the remainder of the experiment with intermittent intravenous injections of the muscular relaxant Flaxedil (gallamine triethiodide). Additionally three of these animals underwent cerebellectomy (one partial and two complete). Long acting 1% Novocaine Tetracaine in oil (Depot Novanaesth) was infiltrated into incised and pressure point areas and manipulative care was maintained in order to avoid painful stimuli. During this time the cats were attached to a respirator.

CONVERGENCE AND INTERACTION OF VESTIBULAR AND DEEP SOMATIC AFFERENTS UPON NEURONS IN THE VESTIBULAR NUCLEI OF THE CAT

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1. In Flaxedil cats 149 neurons in the vestibular nuclei were examined with optic, acoustic, vestibular (labyrinthine polarization) and adequate somatosensory stimuli.

2. 128 neurons, which were *fully examined*, were *analyzed* for their patterns of response. 126 units responded to vestibular stimuli, *104 of these to somatic and vestibular*. 2 neurons responded to somatic stimuli exclusively and none to optic or acoustic.

3. The vestibular results support the concept that the anatomically defined intervestibular (commissural) fibres are functionally significant. The probable semicircular canal or otolith origins of the various vestibular responses are discussed.

4. The somatic influence was almost joint movement specific. Evidence gathered from animals submitted to cerebellectomy or barbiturate anaesthesia supports the concept of a direct proprioceptive somatosensory influence upon the vestibular nuclei.

5. The possible significance of the findings concerning postural and oculomotor mechanisms is discussed.

Phylogenetically the primary purpose of the vestibular apparatus is to regulate body position. This function has been clearly demonstrated in fish by von Holst (1950). In higher vertebrates this regulation of body position becomes more complicated as the neck allows for a greater degree of independent head movement. Thus, in higher forms, the vestibular apparatus informs the central nervous system only with respect to head position and not body position.

It seems reasonable, therefore, to expect a close somato-vestibular in-

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[1] Present address: Dpt. Otolaryng. Stanford University.

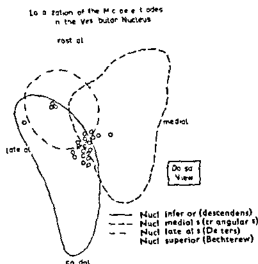


Fig. 1 The circles in the diagram represent the points through which the microelectrodes entered the nuclei The exploration included the entire depth of the nuclei Note that most of the microelectrode recordings were obtained from the medial and descending nuclei where they border one another

A *Neuron Selection*

The area from whence the neurons were obtained (Fig 1) was selected during earlier pilot experiments as a location relatively wealthy in vestibulo somatic convergence Most needle tracts were in the medial and descending nuclei where they border one another In this region unresponsive units were estimated to be less than 5% These unresponsive neurons were not included in the analysis

B *Methods of Stimulation*

1 *Acoustic*

Presumably the acoustic stimulation (hand claps and whistles) was sufficient to have evoked responses despite the fact that the external ear canals were closed by the stereotaxic ear plugs since this same method had been previously employed successfully in eliciting neuronal responses in the reticular system (Bell Sierra Buendia & Segundo 1964 Scheibel Scheibel Mollica & Moruzzi 1955)

2 *Somatic sensory*

When joint movement modified neuronal activity, muscle pressure and fur blowing stimuli were rechecked in the area to rule out possible error It is possible that relatively large joint excursions might have modified the positions of neighbouring joints but care was taken to avoid this Furthermore at times the neurons responded to just one joint of the extremity, or reacted in the opposite manner to movement of the neighbouring joint

Four other intact cats were prepared in a similar manner except that the anesthetic used was the barbiturate Evipan (hexobarbitone) in a dosage of 70 mg per kg of body weight.

Insulated electrolytically pointed (Green 1958) steel microelectrodes 0.3 mm in diameter with tips of 1 to 4 microns were stereotaxically implanted in the left vestibular nucleus through the intact cerebellum. Co-ordinates were obtained from the atlas of Snider & Niemer (1961).

The neurons were subjected to the following stimuli.—Visual: Diffuse white light directed onto open eyes. Both continuous and intermittent illumination with light and dark phases of equal duration. Acoustic: Hand claps or whistles. Vestibular: Weak galvanic current (between 0.05 and 0.12 mA) delivered through the round window membrane electrodes. Somatic: *Included blowing on the fur, gently touching the skin, deep muscle* pressure and joint movement. The neck movement was accomplished while the cat's head was fixed in the stereotaxic apparatus by moving the box upon which the animal's body rested from side to side.

The location of only those neurons responding to at least one of the above stimuli were routinely thoroughly documented.

A six beam cathode ray oscillograph was used to record simultaneously neuronal activity, E.E.G., E.K.G., photocell record of light stimulation and pick-up from the microphone monitoring the acoustic stimuli. Neuronal responses could be photographed at will.

First the lowest, then the highest points from each of the microelectrode tracts from whence neurons were recorded were marked by passing a current through the microelectrode tip for 5 seconds using a 4.5 volt battery. This produced a minute electrolytic lesion in the tissue at the tip of the microelectrode and at the same time deposited a small amount of iron at that point.

Upon completion of the experiment the animals were anesthetized and intravitally perfused with 100 cc of warm saline followed by 300 to 400 cc of 10 per cent formalin solution. The medulla and cerebellum were removed for histopathological study.

The brains were serially sectioned to 25 mμ thickness. Alternate sections were stained by the Prussian blue method and by cresyl violet. Thus the ferric iron deposited in the tissue was identified with the former stain while the latter stain permitted anatomical definition. The location of those neurons lying between the highest and lowest units was readily determined by their known distances from the marked points.

COMMENT

In order that the conclusions in the discussion may be viewed in proper perspective we shall comment upon neuron selection and methods of stimulation.

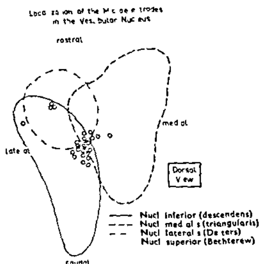


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3 *Galvanic vestibular stimulation*

Galvanic current is not a natural (adequate) stimulus to sensory organs, nevertheless, the effect upon discharges carried in single fibres from the horizontal semicircular canals has been shown to be essentially summative with those of ipsilateral rotational acceleration (Lowenstein, 1955) At the low range of stimulus intensity used in this investigation, galvanic current has been found to be no longer effective centrally following section of the eighth nerve (Spiegel & Scala, 1943, de Vito, Brusa & Arduini, 1956) We do not know the peripheral mechanism by which it produces a response, but probably all portions of the vestibular labyrinth are stimulated It does provide a stream of afferent impulses of "breakshock" character permitting latency analysis, and allows separation of ipsilateral and contralateral effects of the labyrinth upon the vestibular nuclei

The possibility of the current stimulating the cochlea is of no consequence, since there has not been any anatomical or electrophysiological evidence that cochlear fibres end in vestibular nuclei Furthermore, the natural acoustic stimuli in this experiment did not influence neurons in the vestibular nucleus

RESULTS AND COMMENTS

I *Intact Flaxedil Preparations*

A *Histology*

Only three of the 152 responsive neurons from these 12 cats were situated outside of the vestibular nucleus The locations of the needle tracts in the vestibular nuclei are illustrated in Fig 1

Of the 149 vestibular neurons obtained, 78 were located in the descending vestibular nucleus, 53 in the medial nucleus and 18 in the lateral (Deiters') nucleus The majority of these neurons were close to the border area between the descending and medial nuclei The entire depth of these nuclei were explored in the areas indicated (Fig 1) There was no significant response pattern variation from area to area, therefore, the exact points where each neuron was located are not indicated

B *Spontaneous Activity*

All save two neurons were spontaneously active, which is in agreement with previous results, for both the vestibular nucleus (Adrian, 1943, Duensing & Schaefer, 1958 de Vito, Brusa & Arduini 1956) and the vestibular nerve (Gernandt, 1949, Lowenstein, 1955, Lowenstein & Sand, 1940, Ross, 1936) Generally the rate of spontaneous discharge varied between 15 and 30 per second however, the range varied from 0 5 to 90 per second

C Stutter Neurons

Most neurons discharged in a relatively regular manner, but it appeared that there were a few other patterns One distinct pattern consisted of bursts of neuronal activity (stutter) usually in groups of 2 to 4 This was noted in 16 instances (10 ı%), and could invariably be modified by effective stimuli

These neurons were lasting in nature, and it was therefore felt that we were not dealing with 'injured units After effects of anesthesia in the flaxedil cat cannot however be excluded as a possible cause of this stutter pattern

D Unresponsive Neurons

A number of units not included in this series did not respond to any stimulus despite histological confirmation that they were within the vestibular nucleus There were other unresponsive neurons located in the vestibular nuclei but their positions and numbers were not routinely noted Some of these may possibly have been injured units

It is not possible to correlate this group of neurons with that population noted anatomically to be devoid of primary vestibular or spino vestibular afferent endings (Pompeiano & Brodal 1957 Walberg Bowsher & Brodal 1958) because their exact positions within the vestibular nuclei were not routinely established

E Neuronal Responses According to Sense Modality

128 of the 149 responsive neurons located in the vestibular nuclei permitted complete evaluation and therefore the following analysis is based on these 128 units

1 Optic and acoustic

No neurons responded There is no anatomical evidence that optic or acoustic afferents end in the vestibular nuclei Chang & Wu (1959) recorded responses to optic stimuli from units in the toad s vestibular nucleus with latencies of about 300 msec They did not however mention histological confirmation of their microelectrode tip location Ohm (1943) postulated that the vestibular nucleus is a center necessary for the optokinetic response however there is no experimental evidence to substantiate his hypothesis

2 Vestibular

Of the 128 neurons suitable for complete analysis 126 responded to labyrinthine polarization All responses were "specific" in nature according to the criteria discussed elsewhere (Kornhuber & da Fonseca 1964)

Latency times following an inhibiting labyrinthine stimulus were difficult to determine for those neurons which were not very active spontaneously Latency times taken from relatively slow film (10 cm sec) permitted definition for the most rapidly responding neurons to less than

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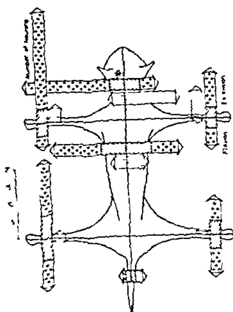


Fig. 3. Patterns of neuronal responses in the left vestibular nuclei to joint movement. (+) signifies activation, (−) inhibition and the total shaded area represents activation in both directions. Number of neurons influenced can be calculated with the use of the scale at lower left. See text for further comments.

The second bar in Fig. 2 represents neurons which responded in a "mirror image" manner to the first type. This rare type has also been observed following physiological labyrinthine stimulation (Duensing & Schaefer, 1959).

Whereas the first and second bars contain neurons which responded in

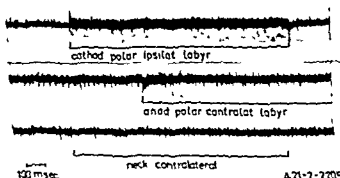


Fig. 4. Vestibulo-somatosensory convergence from a neuron in the descending vestibular nucleus. This combination of ipsilateral cathodic activation and anodic inhibition with activation by ipsilateral neck movement represents the most common vestibulo-somatic convergence noted. Note the rebound activation following anodic inhibition. There was no other somatosensory influence.

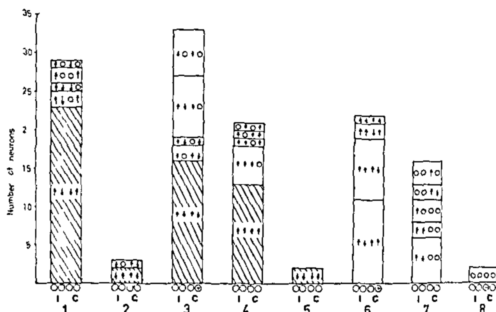


Fig. 2. Activation (↑) and inhibition (↓) patterns of vestibular neuronal responses to ipsilateral (i) and contralateral (c) cathodic (−) and anodic (+) labyrinthine polarization. 0 signifies no response. See text for further description.

1.5 msec. Of 92 neurons so analyzed, 48 were "immediately" activated (i.e. < 1.5 msec, Figs. 4 and 7), 46 following ipsilateral polarization and 17 following contralateral polarization. Faster sweep (66.7 cm/sec) permitted exact latency determinations for other neurons. The type of rapidly responding neurons (referred to above), were found to vary in latency between 0.5 and 0.7 msec following ipsilateral labyrinthine stimulation whereas they varied between 0.7 and 0.9 msec following contralateral stimulation.

Increasing of the polarizing current (as much as four-fold) was found almost invariably to simply increase the strength of the response. Stronger galvanic current infrequently reversed the stimulus response: what previously, at lower current strength, was an inhibiting stimulus became an activating stimulus, the reverse situation was never noted.

This reversal phenomenon, dependent upon higher currents, could be due to additional convergence of afferents from other labyrinthine receptors, resulting in an overall activation of the neuron in question.

The neurons were divided into two main categories according to their response to labyrinthine polarization, that is, direction dependent and direction independent (Fig. 2).

Direction-dependent vestibular responses. This term implies that the responses changed with the reversal of the polarizing current (Figs. 4, 5, 6 and 7).

The neurons in the first three bars in Fig. 2 are of this nature. The most common neuronal response (bar 1) was ipsilateral cathodic activation and anodic inhibition with the opposite response contralaterally (Fig. 5).

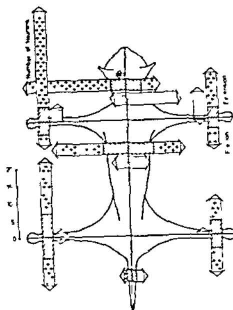


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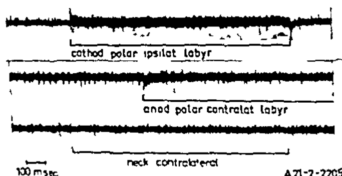


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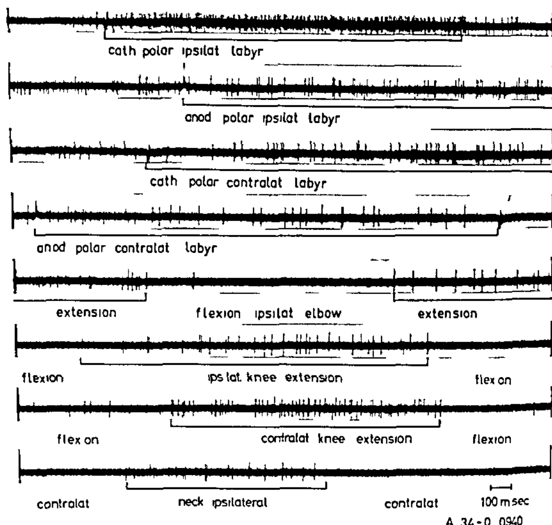


Fig. Vestibulo-somatosensory convergence in a neuron from the border area of the descending and medial vestibular nuclei (Fig. 1). The vestibular response was of the most common type (Fig. 2, bar 1). Note the widespread distribution of joint movement influence.

the opposite manner to stimulation of either labyrinth; the third bar represents units which responded in the same way bilaterally (Fig. 6).

The most frequent neuronal response in the vestibular nuclei (bar 1, Fig. 2) to cathodic galvanic labyrinthine stimulation is the same as that produced by stimulation of the lateral semicircular canal by ipsilateral rotational acceleration or hot calorization (Adrian 1943, Duensing & Schaefer 1958, Eckel 1954, Gernandt 1949, de Vito, Brusa & Arduini 1956). Further, this common galvanic response is compatible to the known fact that stimulation of the lateral semicircular canals in man using warm calorization on one side and cold calorization on the other provokes a "summative" horizontal nystagmus (Aschan & Bergstedt 1955). Responses similar to those shown in bar 1 should also be expected from the vertical semicircular canals with lateral head tilting.

This direction preference of neuronal responses (Fig. 2, bar 1) has also

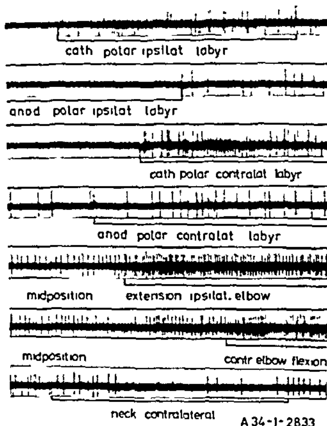


Fig. 6. Somatosensory-vestibular convergence in a neuron located in the caudo-medial portion of the lateral (Deiters') nucleus. Response to labyrinthine stimulus *belongs to* that group of neurons in Fig. 2, bar 3. Elbow movement exerted a reciprocal influence, that is neuronal activation by both ipsilateral extension and contralateral flexion.

been noted in the premotor and motor cortex of the cat (Kornhuber & Aschoff, 1964). Conversely, neurons in the vestibular cortex (Kornhuber & da Fonseca, 1964) and the reticular formation of the brainstem do not indicate this relationship (Duensing & Schaefer, 1957, Gernandt & Thulin, 1952).

The neurons in bar 3 of Fig. 2 could represent the symmetrical type of central response which one might expect from the otoliths, which, according to von Holst (1950), act summatively, or with forward and backward head tilting in the vertical plane, as a result of bilateral symmetrical stimulation of the vertical semicircular canals.

Direction independent vestibular responses. This term implies a fixed neuronal response regardless of the direction of the polarizing current (bars 4 and 5 in Fig. 2). The most frequent response was direction-independent activation. Direction independent inhibition was infrequent.

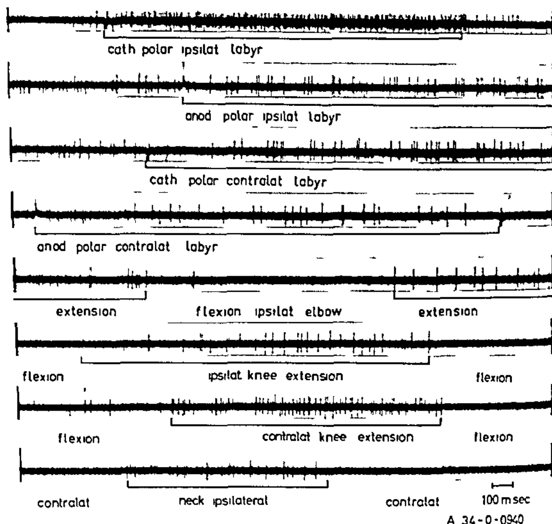


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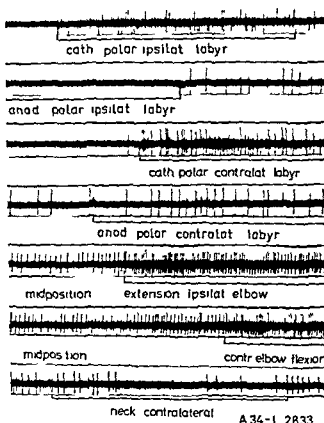


FIG 6 Somatosensory vestibular convergence in a neuron located in the caudo medial portion of the lateral (Deiters) nucleus Response to labyrinthine stimulus belongs to that group of neurons in Fig 2 bar 3 Elbow movement exerted a reciprocal influence that is neuronal activation by both ipsilateral extension and contralateral flexion

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Direction independent vestibular responses This term implies a fixed neuronal response regardless of the direction of the polarizing current (bars 4 and 5 in Fig 2) The most frequent response was direction independent activation Direction independent inhibition was infrequent

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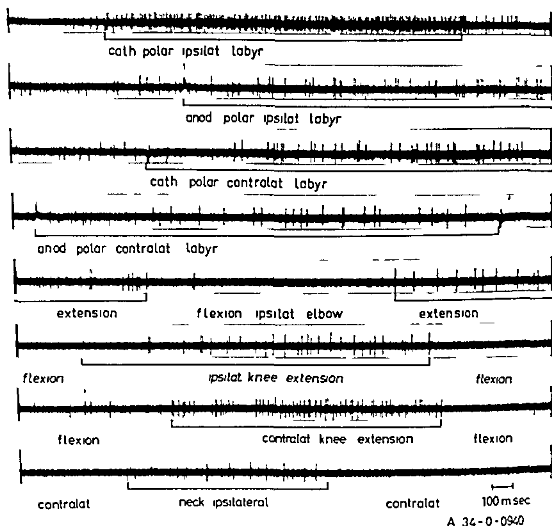


Fig. 5. Vestibulo-somatosensory convergence in a neuron from the border area of the descending and medial vestibular nuclei (Fig. 1). The vestibular response was of the most common type (Fig. 2, bar 1). Note the widespread distribution of joint movement influence.

the opposite manner to stimulation of either labyrinth, the third bar represents units which responded in the same way bilaterally (Fig. 6).

The most frequent neuronal response in the vestibular nuclei (bar 1, Fig. 2) to cathodic galvanic labyrinthine stimulation is the same as that produced by stimulation of the lateral semicircular canal by ipsilateral rotational acceleration or hot calorization (Adrian, 1943, Duensing & Schaefer, 1958, Eckel, 1954, Gernandt, 1949, de Vito, Brusa & Arduini 1956). Further, this common galvanic response is comparable to the known fact that stimulation of the lateral semicircular canals in man using warm calorization on one side and cold calorization on the other, provokes a "summative" horizontal nystagmus (Aschan & Bergstedt, 1955). Responses similar to those shown in bar 1 should also be expected from the vertical semicircular canals with lateral head tilting.

This direction preference of neuronal responses (Fig. 2, bar 1) has also

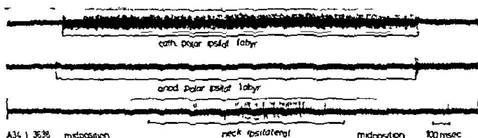


Fig. 7. Vestibulo-somatosensory convergence in 2 simultaneously recorded units from the medial vestibular nucleus. Note the opposite effects that the stimuli have upon the neurons in the upper and lower traces. No further source of somatosensory influence could be found for either neuron.

the findings of Kornhuber & Aschoff (1964) in the premotor and motor cortex of the cat.

The exteroceptive system was rarely represented in the vestibular nuclei, although it has been shown to effect a wide influence upon neurons of the reticular system (Bach-y-Rita, 1964, Bell, Sierra, Buendia & Segundo, 1964, Potthoff & Burandt, 1964, Scheibel, Scheibel, Mollica & Moruzzi, 1955). It is known that the exteroceptive system plays an important role in skilled aimed movements. It would seem from this study that it does not directly exert a prominent effect in vestibular reflex postural adjustments.

According to Henatsch (1965), Flaxedil does not abolish muscle spindle effects and therefore cannot be wholly implicated in explaining why muscle pressure was not an effective stimulus.

Giaquinto, Pompeiano & Santini (1963) showed that there were no neuronal responses in Deiters' nucleus following the electrical stimulation of group Ia nerve fibres which arise exclusively from muscle spindles. This is in agreement with our negative results with muscle pressure. Deiters' units did respond to groups II and III afferent fibre stimulation.

According to the anatomical measurements of afferent fibres from joints (Skoglund 1956), the myelinated fibres belong mainly to group II. Since it is known that the joint afferents travel together with the cutaneous and muscle nerves, the findings of Giaquinto, Pompeiano & Santini (1963) could be in agreement with our results concerning the great preponderance of joint influence.

Approximately 40% of the units were influenced by vertebral movement alone, 40% by both vertebral and extremity joint movement and 20% by movement of the extremities only.

Of the neurons responding to joint movement, approximately 45% were influenced by neck movement. Of these 45%, 50% were influenced by neck movement alone, and 74% responded in a reciprocal manner. Further, of the reciprocally influenced neurons, there were 78% activated by ipsilateral movement and/or inhibited by contralateral movement, significantly outnumbering the 22% influenced in the opposite manner.

It seems reasonable that some neurons should function in this manner, indicating simply that some change has taken place, rather than indicating specifically in which direction These responses were less frequently noted with natural stimulation (Duensing & Schaefer, 1958, Gernandt, 1949), and since we noted that with higher current strengths (0 5–1 0 mA,) an inhibition was reversed to an activation, we feel that the number of units in Fig 2, bar 4, may represent an exaggeration

From Duensing & Schaefer's (1959) investigation, it appears as though neurons in the vestibular nuclei receive converging impulses from more than one labyrinthine receptor. According to Koella's (1950) results, afferents from otolith organs and the semicircular canals converge in the regulation of eye movements If excitatory and inhibitory transmission were equally effective, one would normally expect more frequently an overall activation of the neuron with a convergence of activating and inhibitory influences, since, from the relatively low resting level of activity, the potential range of activation is much greater than the potential range of inhibition The responses seen in bar 6 of Fig 2 could also result from this mechanism

Galvanic stimulation of individual labyrinthine receptors would help to clarify this problem

Mixed responses Bar 6 neurons are in part similar to both direction-dependent and direction-independent responses

Unilabyrinthine responses The majority of units in bar 7 were influenced by the ipsilateral labyrinth It is not possible to decide definitely where they fit into the main types, although most could be placed in either bar 1 or bar 3

3 *Somatic*

106 of the 128 neurons fully analyzed for the labyrinthine influence responded to somatic stimulation Two of the 128 neurons responded only to somatic stimuli Fig 3 is a diagrammatic representation of the somatic responses Exact latency times for responses could not be studied due to the mechanical nature of the stimulus However, it can be said that all answers were immediate and complied with the criteria set forth earlier for "specific" responses (Kornhuber & da Fonseca, 1964) (Figs 4–7)

Most of the neuronal responses were excitatory (Fig 3) as has been noted in Deiters' units in intact and cerebellectomized cats following electrical stimulation of peripheral nerves (Giaquinto, Pompeiano & Santini, 1963, Pompeiano & Cotti 1959, Wilson, Kato & Thomas 1965)

Of the 106 responsive neurons, 103 reacted to joint movement (Fig 3) and only 3 to exteroceptive somatic stimulation Thus the somatic response was *modality specific* Muscle pressure was not effective in eliciting responses

The great preponderance of deep somatic afferent influences agrees with



Fig 9 Semi-diagrammatic illustration of the concept of vestibulo-somatosensory antagonism Movement to position I does not provoke a motor response due to the cancellation of vestibular and proprioceptive neck influences (antagonism) Unopposed labyrinthine influence in position II results in adjusting reflex motor reactions Unchallenged neck influence in position III again results in appropriate motor adjustments

ipsilateral forelimb than by extension of the contralateral forelimb (10) In the ipsilateral forelimb, extension resulted in unit activation far more frequently than flexion In some neurons there was activation by ipsilateral forelimb extension or activation by contralateral forelimb flexion that is a reciprocal effect (Fig 6)

Wilson, Kato & Thomas (1965) have shown that there is a more prominent ipsilateral effect on units in Deiters' nucleus secondary to electrical stimulation of peripheral nerves

We noted that two simultaneously recorded neurons (Fig 7), despite their obvious intimate juxtaposition, can be affected in different manners by the same stimulus

F *Convergence and Interaction*

Of the 128 neurons suitable for analysis, 104 (81%) units responded to both labyrinthine and somatic stimulation (Figs 4–7) Three of these 104 converging neurons responded to exteroceptive stimuli and 101 to joint movement

Interaction between the labyrinthine and somatic responses was investigated in 36 neurons The results were almost invariably summative However when a strong labyrinthine activation was combined with an activating somatic stimulus, there was no further increase in the rate of neuronal activity beyond that produced by the labyrinthine polarization alone ("occlusion") On a few occasions complex interaction was observed

The results of this investigation coincide with Sherrington's (1906) concept of the proprioceptive system, wherein the labyrinths and proprioceptors of the rest of the body work in close cooperation in the regulation of postural motor mechanisms

II *Barbiturate Preparations*

It was more difficult to locate vestibular neurons in the four cats under barbiturate anaesthesia and the 23 units obtained had lower spontaneous discharge rates However, 21 of the 23 responded to ipsilateral labyrinthine polarization and 14 to contralateral stimulation Neuronal responses were produced by joint movement as well

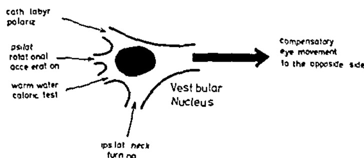


Fig. 8. Contralateral compensatory eye movements resulting from a variety of lateral semicircular canal stimuli and neck movement stimulation all working through the vestibular nucleus.

Our findings of an almost exclusively deep somatosensory influence upon vestibular neurons agree with the known facts concerning the influence that the vestibular system has upon postural motor mechanisms. Sherrington (1898) and Magnus (1924) provided ample proof that reflex postural adjustments require impulses from deep receptors. Philipszoon & Bos (1963) showed that the section of the spinal cord above C1 abolished neck torsion nystagmus, Magnus & Storm van Leeuwen (1914) produced a deficit in cats somewhat resembling a bilateral labyrinthectomy by cutting the dorsal roots of C1, C2 and C3, and Cohen (1961) noted an even more marked labyrinthine-like deficit in monkeys following section or local anesthetization of the C1, C2 and C3 dorsal roots. Furthermore, McCouch, Deering & Ling (1951) demonstrated that the receptors for tonic neck reflexes appeared to be exclusively located within the C1, C2 and C3 *joints*. Thus it would appear that, from the body as a whole, and (in higher animals) from the neck in particular, the joint receptors play a major role in supplying postural information to the vestibular nuclei.

On 114 occasions movement of the *proximal* three joints of the extremities modified neuronal activity, whereas only 25 *peripheral* joint movements were found to be effective. Neuronal responses to joint movement can be seen in Figs. 4–7.

The preponderance of *proximal* joint influence upon the neurons was significant. That this finding is the opposite to that noted in the motor cerebral cortex (Kornhuber & Aschoff, 1964) is interesting in that postural sensibility loss due to cortical lesions is more marked in the peripheral joints (Bergmark, 1909). As well, the proximal joints have been shown to be far more sensitive than the distal joints both with respect to distance and rate of the movement stimulus (Gardner, 1950).

Our findings, in combination with this information, fit well with the fact that the necessarily fine peripheral joint movements in higher animals are a process highly dependent upon cortical function, whereas positional reflexes are more dependent upon subcortical structures with the vestibular nuclei playing a prominent role.

Significantly more neurons (28) were activated by extension of the



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III. *Cerebellectomy*

A partial cerebellectomy was carried out on 1 Flaxedil animal. This consisted of suction ablation of lobules IV and V (Larsell's (1953) classification) of the anterior vermis, lobules VI and VII of the posterior vermis, and a portion of the fastigial nuclei. The 10 neurons studied were located in the descending and medial vestibular nuclei, where the two nuclei border one another. Eight of the units responded to both labyrinthine and joint stimulation, while two responded to vestibular stimulation alone. Similarly located neurons from two completely cerebellectomized cats responded to both joint movement and/or, labyrinthine polarization.

FINAL COMMENTS

A. *Crossed Vestibular Influence*

Gernandt & Thulin (1952) were unable to demonstrate crossed activity in Deiters' nucleus during natural adequate angular stimulation. Gernandt, Iranyi & Livingston (1959) noted that, following electrical stimulation of the peripheral vestibular nerve branches, no evoked potentials could be recorded throughout most of the contralateral vestibular nuclei. Thus Gernandt (1960) felt that the commissural fibres did not play " any significant physiological function unless perhaps it may be inhibitory".

DeVito, Brusa & Arduini (1956), recording exclusively from Deiters' nucleus in the cat, found a great deal of crossed activity within the vestibular system. The specificity of the contralateral vestibular effects in our experiments were unequivocal and in complete agreement. The question remaining concerns the routes taken by these contralateral impulses.

There has been a great deal of work and speculation devoted to the question of the functional significance of the anatomically defined (Cajal, 1909–11, *Ferraro, Pacella & Barrera*, 1940, Gernandt & Thulin, 1952, Rasmussen, 1932) commissural fibres connecting the vestibular nuclei. Brodal, Pompeiano & Walberg (1962) wrote: "The anatomical data on the presence of fibres interconnecting the two lateral vestibular nuclei are inconclusive. There is no anatomical or electro-physiological evidence indicating that primary vestibular fibres cross directly to make their first synapse in the contralateral vestibular nucleus."

Unlike deVito, Brusa & Arduini (1956), we found that contralateral labyrinthine stimulation still influenced some units despite high doses of a barbiturate (Evipan). Of greater significance are the comparisons of latencies between ipsilateral and contralateral labyrinthine stimulation resulting in neuronal activation in Flaxedil preparations. *Regardless* of the actual mechanism by which galvanic labyrinthine polarization eventually leads to neuronal excitation, the variation between the most rapid ipsilateral effect (0.5 to 0.7 msec) and the most rapid contralateral effect (0.7 to 0.9 msec) was just 0.2 to 0.4 msec. Assuming a similar activating

mechanism bilaterally, this difference, based on measurements of synaptic delay (Bishop & O'Leary, 1938, Lorente de Nó, 1938, Renshaw, 1940), would not allow enough time for an additional synapse over and above that which may occur in the vestibular nucleus, despite the fact that these latencies were taken from different neurons We feel this evidence supports the concept that intravestibular commissural fibres play an active role in vestibular mechanisms

The longer latency ipsilateral responses correspond with the anatomical findings of accumulations of neurons in the vestibular nuclei without primary afferent fibres from the vestibular nerve (Walberg, Bowsher & Brodal, 1958) These longer latency responses could be due to secondary responses from the vestibular nuclei or cerebellar and reticular systems

B *Mechanism of Spino-Vestibular Influence*

The specific integration which we have demonstrated, regardless of the exact route taken by the impulses, appears to be rapid enough to be of significance in reflex postural adjustments

Dumont (1960 and 1964) believed that the somatic influence she noted in the vestibular nucleus, following radial nerve stimulation, was "nociceptive" in nature and nonspecific in effect, arriving secondarily via the reticular formation Pompeiano & Cotti (1959) suggested that somatic afferent impulses influence neurons in Deiters' nucleus indirectly via the cerebellum On the basis of Pompeiano's results, Brodal, Pompeiano & Walberg (1962) wrote These features may explain the convergence of impulses from various parts of the body onto a single unit of Deiters nucleus the convergence actually occurring in the cerebellar cortex"

The following evidence supports the view that somatic influence has a direct effect upon some units in the vestibular nucleus (1) Spino vestibular fibres have been found to terminate in the lateral, medial and descending vestibular nuclei (Corbin & Hinsey, 1935, Mehler, Feferman & Nauta, 1960, Pompeiano & Brodal, 1957) and there is ample evidence that there are true internuncials in the medial and descending nuclei (Cajal, 1909–11, Lorente de Nó 1933) (2) We found that large doses of barbiturates did not eliminate the effect of joint movements, and (3) that cerebellectomy did not abolish the somatic influence upon vestibular units (4) Wilson, Kato & Thomas (1965) have shown that units in Deiters' nucleus in cerebellectomized cats responded to peripheral nerve stimulation

The possibility that some somatic impulses first pass through the reticular formation before reaching the vestibular nucleus cannot be excluded However in a similarly constructed parallel study in this laboratory, Potthoff & Burandt (1964) found far fewer neuronal responses to joint movement in the bulbar and pontine reticular formation of Flaxedil prepared cats Other microelectrode studies as well within the reticular formation have yielded very little in the way of joint responses (Bach y Rita,

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proprioceptive neck influence informs the central nervous system of the incompatible body position again giving rise to compensatory movements.

Asymmetrical vestibular reflexes upon the extremities during rapid tilting motion of the entire animal were demonstrated by McNally & Tait (1925), and Tait & McNally (1925) in the frog and by Rademaker & Garcin (1933) in dog and man. The known cervical reflexes upon the extremities during lateral head tilting following bilateral labyrinthectomy (Magnus 1924) are exactly opposite to the vestibular reactions of the extremities during lateral tilt of the entire animal. This antagonism between neck and vestibular influences upon postural motor mechanisms was previously postulated by von Holst & Mittelstaedt (1950).

Our results attest further to the intimate cooperation between the vestibular and somato-sensory systems which has been previously demonstrated electrophysiologically by Mickle & Ades (1952) in the cat's vestibular cortex and Kornhuber & Aschoff (1964) in the cat's motor cortex. Recently Fredrickson, Kornhuber & Fige (1965) have demonstrated that somatosensory-vestibular convergence occurs in the primary vestibular receiving area in the monkey's cerebral cortex.

This cortical vestibular receiving area in the primate brain is located in area 2 of the postcentral gyrus and *not* in the temporal lobe as has been so frequently postulated.

ZUSAMMENFASSUNG

1. Bei Katzen in Flaxedil wurden 149 Neurone des *Vestibulariskerns* mit optischen, akustischen, vestibulären (Labyrinthpolarisation) and adaequaten somatosensiblen Reizen untersucht.

2. Bei 128 mit diesen Reizen vollständig untersuchten Neuronen wurden die Antworten ausgewertet: 126 antworten auf vestibularen, davon 104 auf somatischen und *vestibularen Reiz*. 2 Neurone reagierten nur auf somatischen und keines auf optischen oder *akustischen Reiz*.

3. Die Ergebnisse mit vestibularen Reizen unterstutzen die Annahme, dass die anatomisch nachgewiesenen intervestibularen Fasern auch funktionell *bedeutsam* sind. Die *mögliche Herkunft* der verschiedenen vestibularen Antworten von Bogengängen oder *Otolithen* werden *diskutiert*.

4. Somatische Antworten ruhrten fast ausschliesslich von Gelenkbewegungen her. Untersuchungsergebnisse an Katzen mit Kleinhirnexstirpation oder in Barbituratnarkose unterstutzen die Annahme eines direkten *propriozeptiv somatosensiblen* Einflusses auf die Vestibulariskerne.

5. Die *mogliche* Bedeutung der Ergebnisse hinsichtlich des Lagesinns und Regulation der *Augenbewegungen* werden diskutiert.

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1964, Bell, Sierra, Buendia & Segundo, 1964; Scheibel, Scheibel, Mollica & Moruzzi, 1955) Furthermore (Wilson, Kato & Thomas, 1965), the thresholds for vestibular activation by electrical cutaneous stimulation were lower than those associated with the arousal reaction

From the above considerations it seems reasonable to conclude that, besides spino cerebello-vestibular and spino-reticulo-vestibular paths, direct spino-vestibular influence is important to the process of vestibulo somatic afferent integration which is essential to reflex postural mechanisms

C *Reciprocity and Integration*

Some of our comments are speculative, since the labyrinthine stimulus was inadequate (unnatural) and the exact output of the neurons investigated unknown However, it is known that the vestibular nuclei in the area investigated project to the ocular and spinal motor systems (Gernandt Iranyi & Livingston, 1959, Lorente de No, 1933, Pompeiano & Walberg, 1957, Scheibel & Scheibel, 1958, Szentagothai, 1943)

1 *Vestibulo-cervical synergism in oculomotor regulation*

As Fig 8 *indicates, ipsilateral rotational acceleration,* warm water calorization and cathodic labyrinthine polarization, all acting through the vestibular nuclei, are known to produce compensatory eye movements to the opposite side This compensatory movement represents an important stabilizing regulation for visual perception Because we found that ipsilateral cathodic labyrinthine polarization and ipsilateral neck movement activated the same vestibular neurons summatively, we think it reasonable to expect neck and vestibular afferents to act in a summative manner in *compensatory ocular movements*

These results agree with De Kleyn (1921), Koella (1947) and Tinker (1961) who found functional convergence of neck and labyrinthine influences in the regulation of eye movements

2 *Vestibulo-cervical antagonism in postural motor regulation*

Functionally, *central integration of simultaneous information* from the neck and vestibular labyrinths should be expected in order that appropriate *head to body* adjustments be operative

For example, it is clear in position I, Fig 9, that if *the central nervous* system was to consider only the labyrinthine information without considering the simultaneous information from the neck, then some inappropriate body position would be assumed Thus, in effect, the two signals tend to cancel one another (*antagonism*) as they together have informed the central nervous system that the head to body position is compatible On the contrary, if the cat (or person) was to fall (position II) then the unchallenged labyrinthine information would result in appropriate motor adjustments In position III despite the upright head position the pro-

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HEARING IMPAIRMENT AS THE INITIAL SIGN OF POLYARTERITIS NODOSA

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Two cases of polyarteritis nodosa, in which hearing impairment was the initial sign, are reported. Only 8 cases of this type have been described previously. Aural symptoms were present in 5 out of 21 patients. The hearing impairment is a mixture of conductive and perceptive loss. The miraculous effect of steroid therapy upon the systemic symptoms as well as upon the granulomas of the upper airways and the hearing impairment is reported.

A century has passed by since Kussmaul & Maier (1866) first described the symptoms and signs of the disease which they called, according to autopsy findings, periarteritis nodosa, but which here will be called polyarteritis nodosa.

No mention will be made here of the symptomatology of the disease as a whole or of its differentiation from and relation to other mesenchymal diseases involving vasculitis, such as temporal arteritis, rheumatoid arthritis, disseminated lupus erythematosus, dermatomyositis, and diffuse scleroderma. For information in this respect, the reader is referred to the current textbooks of internal medicine and to a recent review by Skouby (1964).

The classical pathological appearance is a widespread involvement of the small arteries throughout the body but especially those in the kidneys, spleen and skeletal muscles. Histological examination shows necrotizing inflammation of the arterial wall, followed by granulation and healing with scar tissue forming a small nodule on the artery. As might be expected, the clinical manifestations are characterized by the secondary aneurysms, thrombi, and haemorrhages in muscles and viscera.

However, it is not uncommon for the disease to occur in atypical varieties with a dominant local target, like that described by McBride (1897). This type manifests itself as granuloma formation and ulceration of the upper airways, usually the nose, sometimes involving widespread destruction of the face, but as a link in generalized polyarteritis nodosa. The disease is [illegible] granulomatosis (Nieberding Schiff



Fig. 1. Patient with severe nasal and gingival granulomas before and after 2 weeks on prednisone therapy.

& Harmeling, 1963, Wegener, 1939). Biopsies from the granulation tissue usually show non-specific inflammation. The signs from the upper airways include, apart from epistaxis, nasal stenosis, coughing, and haemoptysis, also otitis media and hearing impairment.

From the literature from the period 1897–1957, Blatt *et al.* (1959) collected 124 cases of Wegener's granulomatosis. Out of this number 18 had aural complaints in the course of their disease, and in 6 cases otitis and hearing impairment were the initial signs. Others have reported a few cases of polyarteritis having aural symptoms (Atkins & Eisman 1959, Brown & Woolner, 1960, Herberts, Hillerdal & Ranström, 1957).

Within the past 6 months, we have had 2 patients whose first sign of polyarteritis nodosa was aural complaints in the form of hearing impairment and pressure inside the ears which made them consult a doctor. We feel prompted to call attention to this rare form of manifestation, in particular as it took 3 and 6 months respectively to arrive at the correct diagnosis. Further, we have included 19 cases of periarteritis nodosa, confirmed by biopsy, from the past 4 years, 3 of whom had hearing impairment, and one case of fluctuating, unilateral hearing impairment in a patient with histologically confirmed temporal arteritis. Finally the effect of steroid therapy upon very large nasal granulomas is demonstrated (Fig. 1).

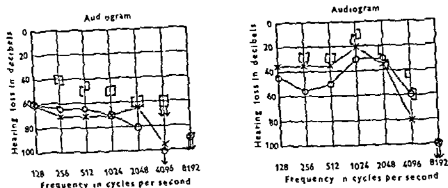


Fig 2 Case 1 Before and after prednisone therapy

Case Reports[1]

Case 1 A woman, aged 54 who had not had any major illnesses in particular no aural diseases and no predisposition to hearing impairment For 2 months prior to admission the patient had been complaining of gradually deteriorating hearing pressure inside the ears and fatigue Primarily her condition was interpreted as catarrhal otitis but paracentesis yielded only very little secretion The hearing was symmetrically impaired, by 60 70 dB, and the hearing loss was predominantly perceptive On admission to an otological department no explanation for the hearing impairment could be found Vestibular tests were normal X rays of the nasal sinuses and chest showed no abnormalities All blood findings were normal apart from the E S R which was 25 mm Conclusion of psychiatric examination hysterical superstructure upon organic hearing impairment As this was not at variance with the impression of the patient in the otological department she was discharged for out patient follow up in view of the elevated E S R During the next 6 months the condition was fluctuating but as a whole not good As the patient was now also complaining of serous rhinitis and nasal stenosis she was admitted to a medical department to be investigated for systemic disease

Laboratory findings Blood pressure 140/90 E S R 104 mm Hb 10 3 g/100 ml serum iron 11 μg 100 ml and transferrin 159 μg/100 ml Coombs test negative W B C 17 000 μl eosinophils 156 μl platelets 500 000 μl Prothrombin proconvertin 140% No L E cell phenomena Serum bilirubin 0 6 mg/100 ml, thymol 0 06 alkaline phosphatases 25–6 7 units 100 ml G P transaminase 2 8–1 0 units/ml W R neg Cold agglutinin < 1 8 Streptococcal agglutinin titre negative Proteinuria of ±1 g 24 hours appeared Serum protein 7 1 g 100 ml with pronounced hypoalbuminaemia and elevated globulins (albumin 2 75 g/100 ml α_2 1 08 g/100 ml 1 59 g 100 ml)

Ophthalmological examination revealed pericorneal infiltrations and conjunctivitis of an endogenous appearance Chest radiography normal Biopsies from muscle and artery showed no pathological changes but biopsy from the kidneys

[1] Our thanks are due to K Brøchner Mortensen A Tybjærg Hansen and J Hess Thaysen heads of Medical Departments A B and P who kindly placed the records at our disposal

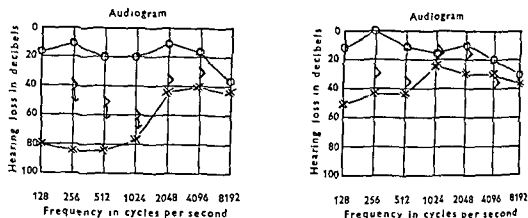


Fig 2 Fluctuations in hearing in a patient with temporal arteritis

revealed necrotizing glomerulitis suggesting polyarteritis nodosa as the most likely diagnosis

Steroid therapy (60 mg prednisone daily) was started, with an almost miraculous effect upon the patient's general condition The E S R fell from 104 to 15 mm, and the serum creatinine returned to normal Her hearing improved considerably (Fig. 2)

After having kept relatively well for more than 6 months, however, the patient suddenly had cerebral haemorrhage and was admitted to another hospital where she died a few days later

Case 2 A woman, aged 48, with a history of allergic rhinitis, bronchitis, and asthma After desensitization with house dust and duck's feathers, however, she had not had further attacks No other otorhinolaryngological diseases and no predisposition to hearing impairment The patient presented herself with shooting pain in the left ear, impaired hearing, and slight dizziness She was found to have a red, thickened drum and meatal eczema The eczema was treated with a hydrocortisone terramycin ointment Subsequent paracentesis yielded some thin, sanguinolent fluid Audiography revealed a mixed, predominantly conductive hearing impairment of 40 dB Caloric test showed slightly reduced reaction on the left No spontaneous or positional nystagmus X-rays of the nasal sinuses showed no abnormalities During the next month the patient deteriorated, complained of fatigue, nausea, and headache Moreover, sanguinolent secretion issued from the right nostril which showed ulceration and granulations on

Table 1 *Diagnoses and number of patients with aural symptoms*

Diagnosis	No of cases	Aural symptoms
Polyarteritis nodosa	15	2
Wegener's granulomatosis	5	2
Temporal arteritis	2	1
Total	22	5

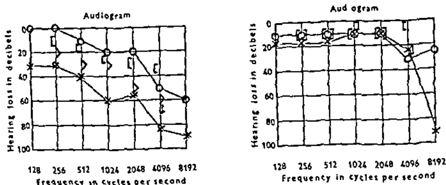


Fig 3 Case 2 Before and after prednisone therapy

the inferior concha The patient was now admitted because of a suspicion of systemic disease, first to an otological and later to a medical department

Laboratory findings Blood pressure 120/75, E S R 86 mm, Hb 11 4 g/100 ml Serum iron 30 μg/100 ml, and transferrin 241 μg/100 ml Platelet, white cell and differential counts normal Prothrombin proconvertin 100% Serum bilirubin 0 4 mg 100 ml thymol 0 07 alkaline phosphatases 8 7 units/100 ml, G P trans aminase 0 6 units ml serum creatinine 0 8 mg/100 ml, W R negative Cold agglutinin titre 1 8 Rose Waaler negative No L E cell phenomena Urine analyses normal No blood in the faeces Serum protein 6 8 g/100 ml with slight hypoalbuminaemia (3 8 g 100 ml) and slightly elevated α_2 (0 73 g/100 ml) X rays of the nasal sinuses showed mucosal thickening, and chest radiography an infiltration in the right lung which on tomography was found to be well defined extending right to the hilus Bronchography failed to afford further information Muscle biopsy showed no abnormalities Skin biopsy revealed slight, non specific inflammation Biopsy from a lymph node revealed non specific reticulosis Repeated biopsies from the nose also showed non specific inflammation until a new specimen, about 3 months after the patient was first seen, revealed severe granulomatous inflammation of the Wegener type

On steroid therapy (40 mg prednisone daily) the patient flourished The E S R dropped from 86 to 33 mm the pulmonary infiltration and blurring of the sinuses regressed the nasal mucosa healed, and the tympanic membrane regained its normal appearance Moreover, the hearing returned almost to normal in a few days (Fig 3)

DISCUSSION

Judging by the literature, hearing impairment is an extremely rare initial sign of polyarteritis nodosa As far as we can trace, only 8 cases are on record With the 2 present cases, this number is brought up to 10 As already mentioned, 5 out of 21 patients with microscopically confirmed polyarteritis nodosa were found to have hearing impairment This corresponds to the incidence found in series where aural symptoms have been reported (Atkins & Eisman, 1959, Blatt *et al*, 1959, Brown & Woolner,

1960, Herberts, Hillerdal & Ranstrom 1957) In all the cases the hearing impairment was a mixture of conductive and perceptive loss It is not affected by ordinary methods of treatment, but improves immediately after institution of steroid medication

The conductive component of the hearing loss may be naturally explained on the basis of the mucosal changes in the middle ear which are concurrent with the changes in the nose and nasal sinuses On autopsy of 2 patients with polyarteritis nodosa Blatt & Lawrence (1961) found serous exudate in the middle ear and fibrinous granulation tissue surrounding the round and oval windows One of the patients exhibited moreover on one side invasion of the granulation tissue through the round window into the vestibule and further to all 3 semicircular canals and into the basal turn of the cochlea

As early as 1937 Rossle described characteristic polyarteritis nodosa changes in an artery of the middle ear mucosa Although further histological studies are not yet available, there is reason to believe that vascular abnormalities are present also in the inner ear similar to the manifestations of this disease in other sites

ZUSAMMENFASSUNG

Es wird uber zwei Fälle von Polyarteritis nodosa mit Gehorschwächung als Initialsymptom berichtet Nur 8 entsprechende Fälle sind fruher veroffentlicht Bei 5 von 21 Patienten zeigten sich Ohrsymptome Die Gehorschwachung besteht aus Schalleitungs und Perzeptionsschwerhorigkeit Die mirakulose Wirkung von Steroidbehandlung auf sowohl Gemeinsymptome und Granulome in oberen Luftwegen als auch auf die Gehorschwächung wird besprochen

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THE RESPONSE OF THE VOCAL FOLDS TO ELECTRICAL STIMULATION OF THE INFERIOR FRONTAL CORTEX OF THE SQUIRREL MONKEY

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Experiments were performed on squirrel monkeys to locate the cortical motor area of the vocal folds and to study their response to an electrical stimulus. The surface of the frontal gyri were electrically stimulated bilaterally, and the cortical area of the vocal folds established. A surgical procedure also was devised to record the mechanical properties of the thyroarytenoid muscle. The muscle was attached to a physiological transducer, and responses quantified by recording the output signal of the transducer on a high frequency inkwriter. The cortical motor area of the thyroarytenoid muscle was found to be in a subdivision of Brodmann's area 6. Bilateral contraction of the vocal folds was obtained by stimulation of either hemisphere, stronger responses were ipsilateral. With glottic closure, respiration ceased, and there was concomitant swallowing which appears to act as an auxiliary respiratory mechanism following asphyxia. Findings also were discussed in relation to phonation.

INTRODUCTION

In 1917, Leyton & Sherrington described a motor cortical area of the vocal folds in primates. Using a faradic stimulus, they observed that the vocal folds of the chimpanzee and gorilla adducted when an electrical stimulus was applied to the anterior and lower part of the facial area of the cortex (frontal gyrus). In the same study, they obtained an emission of sound from the chimpanzee. Smith (1941, 1945) and Kaada (1951) elicited vocalization in monkeys by stimulating the anterior cingular gyrus and banks of the cingulate sulcus. The cingular gyrus was proposed by Popez (Smith, 1945) to be a part of a morphological system consisting of the hypothalamus, the anterior thalamic nuclei, and hippocampus. Excitation of the cingular gyrus produces a complex of responses which are characterized by *expressive or general movements as opposed to specific* muscular actions.

This study was supported by Public Health Service Research Grants from the National Institutes of Neurological Diseases and Blindness (NB-05241 01 and NB 02779 05).

However, in the dog and cat a motor cortical area for the vocal folds was not found (Kaada 1951 Milojevic & Hast, 1964) Vocalization in the cat was elicited by electrical stimulation of the lower brain stem and hypothalamus (Kanai, 1963)

In man, vocalization was evoked upon stimulation of the precentral motor cortex (Penfield & Bordley 1937) In 1938, Penfield found that vocalization could be elicited fom either hemisphere at a point on the precentral Rolandic gyrus between the centers for hand and throat movement Later, Penfield & Rasmussen (1950) demonstrated that vocalization could also be obtained from the supplementary motor area of both cerebral hemispheres This finding was confirmed by others (Lewin & Whitty, 1960)

Although vocalization or vocal fold adduction has been produced in primates by electrical stimulation of the motor cortex previous investigators have not reported quantitative observations of vocal fold response upon excitation of the cerebral cortex

The purpose of this study was to describe and measure the response of the vocal folds in particular the thyroarytenoid muscle, to cortical electrical stimulation of the inferior frontal gyrus of the squirrel monkey

METHODS

Experiments were performed on male and female squirrel monkeys (Saimiri sciureus) of an average body weight of 788 g (range of 650–870 g) Animals were anesthetized with α chloralose (70 mg/kg) given intraperitoneally Initially ether was used to contain the animals for the administration of chloralose

The anesthetized animal was placed in a supine position and a midline scalp incision was made from the *glabella* to the *lambda* Craniotomy was performed exposing the greater surface of the brain from the post central motor region to the supplementary motor area of the frontal pole and most lateral extension of the Sylvian fissure The dura was sectioned and precautions were taken to keep the brain surface warm and moist using a lamp (Tensor No 5975) and by application of a warm (37°C, ±1°) physiological irrigating solution (Baxter Tis U Sol) The animal s body temperature was maintained by a heating pad

A midline neck incision was then made from the level of the hyoid bone to the sternum and tracheotomy at the third or fourth ring was performed

The inferior frontal gyrus was stimulated ipsilaterally and contralaterally and observations of vocal fold movement were obtained sub glottically through a Zeiss operating microscope The recurrent laryngeal nerves were electrically stimulated as well, to distinguish true vocal fold movement from an artifact and to compare vocal fold movement in central and peripheral stimulation

Next a midline incision was made from the thyrohyoid membrane through the thyroid cartilage and cricothyroid ligament One of the laminae

of the thyroid cartilage was incised laterally at the level of the laryngeal sinus, the incision was continued caudally, parallel to the midline incision to the cricoid cartilage The incision was completed by cutting the crico-thyroid membrane and muscle Surgical silk (5-0) was sutured to the incised section of the thyroid cartilage, the point of origin of the thyro arytenoid muscle (true vocal fold) With the thyroid cartilage and vocal fold *in situ*, the other end of the silk was tied to the input probe of a transducer (Statham, G1-16-350). The output of the transducer led to the input of a strain gage coupler (Offner, Type 9803) and was amplified and recorded by an ink-writer (Offner, Type RS Dynograph) The transducer was calibrated in gram weight with metric masses The total response-time of the instrumentation did not exceed 3 msec

The ipsilateral and contralateral surface of the brain was electrically stimulated with square wave pulses from a physiologic stimulator (Grass S-4), with coupled stimulus isolation unit (Grass, SIU-4B), using bipolar shielded platinum electrodes (polar distance, 1 mm) In the preliminary "mapping" of the cortex, animals were stimulated during the interval between inspiration and expiration, and a 10-sec interval was maintained between stimulations Once the motor center of the vocal fold muscle was found, a 5-min interval was maintained between successive stimulations in order to minimize facilitation or extinction effects The duration of each stimulus pulse was 1-2 msec, and trains of stimuli were 1-2 sec In addition, stimulations were varied in frequency and voltage, in order to determine the cortical threshold for contraction of the thyroarytenoid muscle

The premotor and motor cortex of each monkey was systematically explored, and the ipsilateral and contralateral motor area of the vocal fold was plotted on a standard brain diagram, brain diagrams were superimposed and a composite scatter plot was made of the cortical foci of vocal fold response In addition, following each experiment, both laryngeal cortical motor areas were marked by damaging the cortex at the focus of the strongest response, and compared with a brain diagram At the termination of each experiment, the animal was sacrificed, and its brain removed and placed in a 10% solution of formaldehyde

RESULTS

Experiments were repeated with consistency in six squirrel monkeys An isolated vocal fold response was localized on the cortical surface of the inferior frontal gyrus, at an average point 3 1 mm anterior to the lateral cerebral fissure (Sylvius), 7 4 mm rostrad to the lateral basal surface of the frontal lobe, and 3 mm in diameter The plotted foci are shown in Fig 1

The average threshold frequency of cortical stimulation for the intrinsic muscle of the vocal folds (the thyroarytenoid) was 60 pulses sec, reaching maximum contraction at a stimulus frequency of 110 pulses sec The

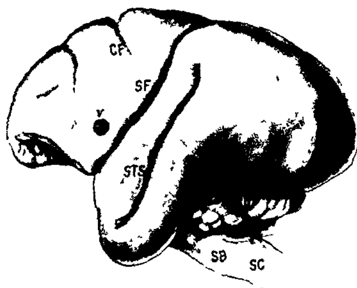


FIG 1 Supero lateral surface of the squirrel monkey brain The stippled area, lettered V, indicates the focus of the vocal folds (thyroarytenoid muscle), *CF* central fissure, *SF*, Sylvian fissure *STS*, superior temporal sulcus, *Cb* cerebellum, *SB* spinal bulb, *SC*, spinal cord

strength of stimulus averaged 3 8 v (threshold) to 10 v, with the ipsilateral cortex predominate for the response of the muscle (Fig 2)

It was observed that, when a train of stimuli of 1–2 sec duration was applied, the ipsilateral vocal fold was first excited in continuous movements of adduction–abduction After approximately 3 sec of stimulation, the contralateral vocal fold joined its mate in synchronous movement After 4–5 sec of stimulation, both cords adducted to the median position, respira-

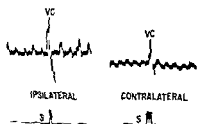


Fig 2

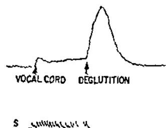


Fig 3

FIG 2 Recordings of the response of the vocal cords (VC)—thyroarytenoid muscle—to an ipsilateral stimulus (S) of 0.5 sec and a contralateral cortical stimulus (S) of 1 sec

FIG 3 Recording of the response of a vocal cord (thyroarytenoid muscle) followed by deglutition The output of the square wave stimulator (S) was recorded by the second channel of the recorder The train of stimuli was 4 sec

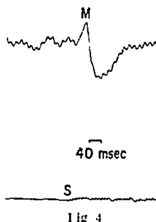


Fig 4

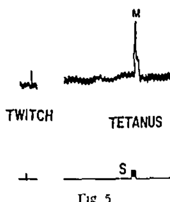


Fig 5

Fig 4 Recording of the thyroarytenoid muscle (M) in response to a single square wave stimulus (S) of 9 V applied to the ipsilateral cortex

Fig 5 Recordings of the response of the thyroarytenoid muscle (M) to peripheral electrical stimulations (S) of the recurrent laryngeal nerve, 1 pulse/sec (twitch) and 100 pulses/sec (tetanus) In this example the duration of each square wave pulse was 0.2 msec at 1 V

tion ceased, and concomitant swallowing followed (Fig 3) During the course of this study abduction of the vocal cords was never observed

An example of measurements made of the response of the thyroarytenoid muscle to a cortical electrical stimulus is shown in Figs 4 and 5 The average *latency* for muscle contraction averaged 16 msec (± 4), the *contraction time* of the muscle (time to peak of contraction from end of latent period) averaged 24 msec (± 6) With peripheral stimulation, the average *tetanus twitch tension ratio* for the thyroarytenoid muscle was 4.5:1 (± 0.7) All of the latter measurements were made with a tetanizing stimulus of 100–110 pulses/sec, pulse-duration of 1 msec, and at an average of 9 V

In addition to the singular response of the thyroarytenoid muscle to cortical stimulation, contraction of extrinsic laryngeal and suprahyoid muscles was observed at various times These responses could be differentiated from the true vocal fold response (Fig 3)

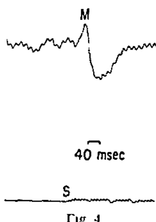
DISCUSSION

In this study, cortical localization of the vocal fold to an area of the inferior frontal gyrus of the primate agreed with findings of Leyton & Sherrington The motor center of the vocal fold specifically localized to a subdivision of Brodmann's area 6 designated as 6bα by the Vogts (Fulton, 1949) This subdivision of area 6 is not only a cortical motor area for the vocal fold muscle but was observed to give rise on stimulation to sustained movements of the tongue lips mandible and pharynx (Fulton, 1949) Thus, although an isolated response of a single muscle, the thyroarytenoid in the present study, could be obtained from a particular

point on the cortex (Chang, Ruch & Ward, 1947), there is an overlapping of cortical fields for various muscle and muscle groups (Bucy, 1949)

In the present study, the muscle group for deglutition was observed to be the most consistent field facilitated on continued stimulation of the cortical focus of the vocal cord According to Fyke & Code (1955), the beginning of swallowing initiates high positive pressure in the pharynx, while negative pressure develops in the esophagus Negative esophageal pressure increases the negative intrathoracic pressure, which is exerted upon the heart, the great blood vessels, the thoracic duct, intrapleural lymph and particularly upon intrapulmonic pressure (Metzer, 1892) During the act of normal inspiration, intrapulmonic pressure temporarily falls below that of the atmosphere If the glottis is closed for a longer period of time, changes in intrapulmonic pressure are much greater Vigorous inspiratory movements may considerably lower the pressure, whereas strong expiratory movements raise intrapulmonic pressure above atmospheric pressure Apparently, deglutition can act as an auxiliary respiratory mechanism in a state of asphyxia A high pressure deglutition wave is transmitted as a normal peristaltic wave over the full length of the esophagus, increasing the negative pressure above and below the bolus In this experiment, deglutition occurred concomitantly with the cessation of respiration and closure of the glottis The latter reflex could be a part of a central protective mechanism, in which repetitive swallowing forces air of the physiological dead space into the lungs, by changing intrathoracic pressure, when there is respiratory asphyxia Doty & Bosma (1956) observed that, "In early asphyxia, most or all of the muscles active in deglutition are recruited into the respiratory effort" With incomplete asphyxia in the monkey action ceased in the diaphragm after two minutes, while swallowing was still excitable in the normal pattern and cyclical respiratory efforts continued in the pharyngeal muscles "By reason of the continual nature of respiration, and the utilization of common pharyngeal passages, the synergies of swallowing and respiration must inevitably interact" (Doty and Bosma 1956)

In this study, the ipsilateral cortex of the monkey was found to be dominant for vocal fold movement This finding is not in disaccordance with that of Penfield and Boldrey for the human As Penfield & Boldrey (1937) have stated, "Vocalization [in the human] is made up of a well formed vowel sound which continues until the patient's breath is exhausted It is quite distinct from grunting which seems to have its representation at a point lower in the Rolandic cortex and nearer the fissure of Sylvius" This latter area has been described by Leyton and Sherrington and others (Fulton) as the 'face' or "second motor" area (Ruch & Fulton, 1960), an area found to dominate ipsilaterally It is within this area that the cortical motor representation for the thyroarytenoid muscle was found Also, in a study of the subcortex of the cat, Kirikae *et al* (1962) found that responses of the ipsilateral thyroarytenoid muscle always were more predominant



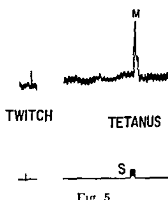


Fig 4

Fig 5

FIG 4 Recording of the thyroarytenoid muscle (*M*) in response to a single square wave stimulus (*S*) of 9 v applied to the ipsilateral cortex

FIG 5 Recordings of the response of the thyroarytenoid muscle (*M*) to peripheral electrical stimulations (*S*) of the recurrent laryngeal nerve, 1 pulse/sec (twitch) and 100 pulses/sec (tetanus) In this example, the duration of each square wave pulse was 0 2 msec at 1 v

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cessant et en même temps il y avait déglutition ce que nous a semblé être un mécanisme respiratoire auxiliaire lors de l'asphyxie De plus nos résultats sont étudiés relativement à la phonation

ZUSAMMENFASSUNG

Es wurden experimentelle Studien an Affen (Saimiri sciureus) durchgeführt, um das motorische Rindengebiet der Stimmfalten zu lokalisieren und die Antwort auf elektrische Reizung zu untersuchen Die oberfläche der Frontalwindungen wurde beiderseits elektrisch gereizt und das Rindengebiet der Stimmfalten dargestellt Ein chirurgischer Fingriff wurde entworfen um die mechanischen Eigenheiten des M thyreo arytenoideus zu registrieren Der Muskel wurde mit einem physiologischen Transducer verbunden und die Quantität der Antworten dargestellt indem das Ausgangssignal des Transducers mit einem für hohe Frequenzen geeigneten Tintenschreiber registriert wurde Die motorische Rindenregion des M thyreo arytenoideus wurde in einem Teil von Brodmann's Area 6 gefunden Bilaterale Kontraktion der Stimmfalten wurde durch Reizung in jeder der beiden Hemisphären erzielt, stärkere Reizantworten waren hingegen ipsilateral Wenn es zu Glottisverschluss kam, erfolgte Aufhören der Atmung Der darauf auftretende Schluckakt scheint ein respiratorischer Hilfsmechanismus zu sein der bei Asphyxie auftritt Die Befunde wurden auch in Beziehung zur Phonation besprochen

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than the contralateral one. In addition, Kirikae *et al.* (1962) and Kanai (1963) found that in the brain stem the vocalization area was bilateral with either area able to elicit bilateral contraction of the vocal folds.

The contraction time of the thyroarytenoid muscle is of singular interest to a theory of phonation since this time is a limiting factor in determining the number of synchronous muscular contractions. Husson (1962) has proposed that the vocal folds can synchronously follow a cortical discharge to at least 500/sec. In studies on the dog, Mårtensson & Skoglund (1964) determined the contraction time of the thyroarytenoid muscle by peripheral electrical stimulation of the recurrent laryngeal nerve; the average contraction time of the thyroarytenoid muscle was 14 msec. With central cortical stimulation the average contraction time was much longer (24 msec). From the results of this and previous studies (Hast, 1961), it is not likely that the thyroarytenoid muscle could synchronously follow a nerve impulse from the brain beyond 60/sec, at which point contractions become fused.

CONCLUSIONS

The following observations and conclusions were made: (1) the cortical motor area of the thyroarytenoid muscle was found to be in a subdivision of Brodmann's area 6 designated as 6bα by Vogt and Vogt. (2) Stimulation of the cortex resulted in stronger contractions of the ipsilateral thyroarytenoid muscle. (3) Bilateral contraction of the vocal folds was achieved by stimulation of either ipsilateral or contralateral cortex. (4) When both cords adducted to the median position, respiration ceased and there was concomitant swallowing. This swallowing, which follows asphyxia, acts as an auxiliary respiratory mechanism by changing the intrathoracic pressure, forcing the air of the physiological dead space into the lungs. (5) In responding to a cortical stimulus the average contraction time of the thyroarytenoid muscle was twice as long (24 msec) as when stimulated peripherally. The question is raised as to the ability of the vocal fold musculature to follow a cortical potential in synchronous contraction beyond a frequency of 60/sec.

RÉSUMÉ

Des expériences ont été pratiquées chez des singes (Saimiri sciureus) afin de localiser la zone corticale motrice des cordes vocales et d'étudier la réponse à un stimulus électrique. La surface des circonvolutions frontales a été stimulée bilatéralement et cette zone corticale établie. Afin de déterminer les propriétés mécaniques du muscle thyro-aryténoïdien, nous l'avons isolé antérieurement et attaché à un transducteur physiologique dont la réponse a été enregistrée sur un appareil à haute fréquence. La zone corticale motrice des cordes vocales a été localisée dans une subdivision de la zone 6 de Brodmann. La stimulation de l'un ou de l'autre hémisphère provoquait la contraction des deux cordes vocales, la réponse la plus forte étant toujours ipsilatérale. La glotte fermée, la respiration

THE USE OF HYPNOSIS IN AUDIOLOGIC ASSESSMENT

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A case was presented to illustrate the use of hypnosis in otology for obtaining precise information relative to diagnosis when such information had been impossible to obtain with standard, as well as with special audiological tests. In this case it appeared imperative to determine threshold sensitivity for pure tones in view of progressive familial deafness. The results point up the fact that hypnosis can be utilized diagnostically in an otological clinic, and that serious consideration should be given to appropriate training of staff members in its use.

Within the past ten years there has been an awakening interest in the technique of hypnosis for medical purposes. Such specialities as obstetrics, dentistry and psychiatry have added it to their armamentarium of diagnostic and therapeutic procedures. Insofar as the field of otorhinolaryngology is concerned, seemingly only meager effort has been expended to explore its possibilities. A few authors have stressed the importance of hypnosis in the treatment of functional hearing loss, but little or no mention is made of its use as a diagnostic procedure (Fowler & Zeckel, 1952, Fowler 1957, Guild, 1959, Kodman & Pattie, 1958, Kroger, 1963).

Recently we have become interested in hypnosis as a diagnostic tool for cases in which other standard procedures have failed to produce a specific result. The purpose of this paper therefore is to report a case of functional deafness which was recently seen in the clinic, and with whom the technique of hypnosis was employed to obtain pure tone and speech reception thresholds.

The patient, a 13-year-old white male, had been admitted to the Kansas School for the Deaf purportedly for failure in school contingent upon a severe bilateral hearing impairment. On admission, he was administered a battery of psychological tests which is standard procedure for all entering students. Intelligence was within normal limits as measured by the Wechsler Intelligence Scale for Children. However, a series of projective-type, personality tests elicited strong indications of emotional disturbance. In addition the standard audiological evaluation at the school had revealed definite signs of functional deafness.

The views expressed herein are those of the authors and do not necessarily reflect the views of Air University, the United States Air Force or the Department of Defense.

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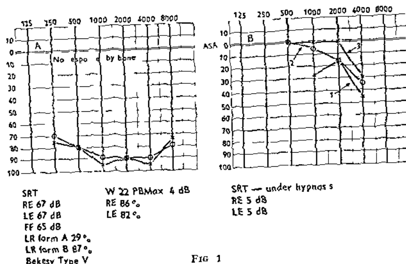


FIG 1

with a 90 dB bilateral hearing loss could not have heard the speech at the *20 dB level* on Form B, and should have obtained a score which was consistent with the Form A results This procedure therefore, definitely indicated that the patient was hearing and understanding speech at a 20 dB level *re* normal hearing in a free field

The above tests had clearly shown that the patient had very little if any hearing loss However it had not been possible even after numerous sessions to get him to respond either to pure tones or to speech at a level which was consistent with the Delayed Feedback and lipreading test results Less than equivocal results had been obtained with the Psycho Galvanic Skin Response test which had been attempted in the interim

In view of the fact that there was a history of familial deafness it was deemed necessary to utilize as many techniques as possible in an all out attempt to determine his absolute threshold This decision seemed particularly imperative in view of his father s perceptive hearing loss which had begun at about age 14 years It was decided therefore to attempt hypnosis since there are several experienced hypnotists on the staff

After having obtained the consent of the parents the first hypnotic session was held This session consisted of repeated induction attempts during which only very light trance states were induced Suggestions for re-entering hypnosis were made

At a second session a few days later, the patient was put into a deep trance after repeated inductions and awakenings Following the first deep trance an SRT was attempted in a free field using monitored live voice A speech reception threshold of 30 dB was obtained Again the patient was placed in a deep trance and instructions given relative to a procedure for responding to pure tones Specifically, he was told to squeeze the hypnotist s hand when the tone was perceived and to relax the grip when it was no

In lieu of the aforementioned, the boy was referred to the Department of Otolaryngology of the Kansas University Medical Center for extensive examination Hearing loss was purported to have been progressive over the past two years, and accompanied by intermittent, high-pitched tinnitus There had been neither ear infections nor exposure to high level noise However, there was a family history of hearing impairment The patient's father had a bilateral, sensory-neural loss which had begun at 14 years of age There was also a maternal uncle with decreased hearing sensitivity A general physical examination showed the patient to be in good health Similarly, the otolaryngic examination was normal

Thereupon, a battery of audiological tests was administered which included pure tone air and bone conduction, Bekesy tracings, speech reception thresholds, auditory discrimination, Doerfler-Stewart, delayed feedback, the Lombard, PGSR audiometry, and special lipreading tests As will be seen in Figure 1 A, the pure-tone air conduction curves were on the average at a 90 dB level through the speech range, and were consonant with previous results There were no responses by bone conduction However, the speech reception thresholds of 67 dB as well as the discrimination scores of 86 and 82 per cent at a PB max of 4 decibels for the right and left ears respectively, were suggestive of functional overlay In addition, the masking of the Doerfler-Stewart Test had interrupted his admitted speech reception threshold of 65 dB in a free field, when the overall level of the noise was approximately 15 dB below the level of the speech Hence, this finding also tended to indicate functional deafness However we were not able to lower his admitted speech threshold with this technique The Bekesy results were Type V with the continuous-tone threshold tracing averaging about 75 dB as compared to an interrupted tone-tracing of 90 dB Thus, although the Bekesy findings were again suggestive of functional deafness, nevertheless, they gave us no indication of his real threshold

In conjunction with the above, the Delayed Feedback Test for each ear with overall masking noise of 80 dB SPL on the contralateral ear produced positive effects indicating either normal hearing through the speech frequencies for each ear or, at most, that he could not have a hearing loss which exceeded 30 dB

Finally, speech reading tests were administered with and without amplification for the purpose of comparing scores, and for observation of behavior under the two conditions This particular device is frequently employed by us in cases of suspected functional deafness Briefly, with the patient in the test chamber and the examiner in the adjoining control room, Form A of the Utley Lipreading Test is administered through the observation window of the two room set-up Next, Form B of the test is given, but this time with low level speech (20 dB level *re* normal threshold) of the test sentences coming through one of the speakers in the test chamber The patient obtained a score of 29 per cent on Form A and 87 per cent on Form B under the described conditions Obviously, an individual

THE INFLUENCE OF MENTAL ACTIVITY AND VISUAL FIXATION UPON CALORIC-INDUCED NYSTAGMUS IN NORMAL SUBJECTS

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The left ear of six normal subjects was irrigated with water at 44°C and the nystagmic response recorded electro-oculographically Three test conditions were employed test condition I, when visual fixation was absent and mental activity reduced, test condition II, when both visual fixation and mental activity were present, test condition III, when mental activity was present but visual fixation was absent Using eight indices of caloric induced nystagmic response a consistent greater response occurred for test condition III This test condition also produced records which were less frequently rated irregular than the records for test condition I Dysrhythmia of nystagmic response still occurs in test condition III

INTRODUCTION

It is over a century ago that Schmiederkam (1868) discovered that nystagmus could be produced by irrigating the ears with water, over a half a century ago that Bárány (1906) developed this caloric test for the clinical examination of vestibular function and over a quarter of a century ago that Jung & Mittermaier (1939) developed electro-oculography for the objective registration of caloric-induced nystagmus This method for recording of caloric-induced nystagmus, frequently termed caloric electro nystagmography, further pointed out the observations which were done over many years during the caloric testing with visual observation of the eyes i e the existence of considerable variability of the recorded nystagmus This variability of response still exists despite the considerable attention that has been paid to the subject by many investigators (Aschan *et al*, 1956 Mahoney *et al* 1957, McLay *et al*, 1957, Carmichael *et al*, 1961, Guedry *et al* 1961, Ladvall, 1961, Collins *et al*, 1961, Hinchcliffe & Voots, 1962 Collins 1962, Collins *et al*, 1962, Collins & Guedry, 1962, McLay, 1962, Sokolovski, 1963)

Although there is a considerable amount of inter-subject variability, there is also an appreciable intra-subject variability. Two of the principal factors which appear to have been responsible for the intra-subject variability are (*a*) degree of mental activity, and (*b*) occurrence or absence of visual fixation The present experiment was designed to investigate the importance of these two factors in normal subjects

longer heard Earphones were then positioned on his head and the test was initiated

Curve 1 of Figure 1 B presents the initial threshold responses for the left ear As shown, these were 25 dB 15 dB and 45 dB for the frequencies 1000 2000 and 4000, respectively Next, the right ear was tested and the threshold determined as shown by curve 2 The left ear was then retested with the resultant improvement as illustrated in curve 3 Rechecks of threshold while the patient was still in deep trance produced no further changes in curves 2 and 3 While still in deep trance the patient was instructed to nod his head "yes" or "no" in the conventional manner to questions which would be asked through the earphones (Hypnotist in the test chamber with patient and tester in the adjoining control room for SRT as well as the preceding pure tone tests) With this procedure SRT's were obtained at a 5 dB level for each ear The results were unequivocal as were those for the pure-tone thresholds

Since this second session had lasted about two hours no attempt was made to measure bone conduction at 4000 Hz However in view of the complaint of the patient of high tone intermittent tinnitus and a negative history of acoustic trauma it seems likely that the bilateral loss at 4000 Hz could be a manifestation of incipient hereditary, sensori neural impairment Appropriate measures have been taken for follow up tests psychotherapy and eventual return to the regular public schools

ZUSAMMENFASSUNG

Die Anwendung von Hypnose in der Ohrenheilkunde wird durch einen Fall dargelegt bei dem es unmoglich war eine genaue Diagnose mit den ublichen und speziellen Testverfahren zu stellen In dem besprochenen Fall schien es wichtig auf Grund fortgeschrittener familiarer Taubheit die Schwellensensitivitat fur reine Tone zu bestimmen Die Ergebnisse zeigen dass die Hypnosetechnik fur diagnostische Zwecke in der Ohrenklinik benutzt werden kann und dass man die entsprechende Heranbildung von Personal auf dem Gebiete der Hypnose ernstlich erwagen sollte

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Apparatus

The thermal stimulus was provided by a thermostatically controlled water bath to give a temperature of 44°C at the outlet of the tubing leading from the bath to the subject's external acoustic meatus The electro oculo graphic recording apparatus was that described by McLay *et al* (1958) This equipment has a coupling time constant of ten seconds which ensures an undistorted recording of the nystagmic wave form Paper speed was 1 cm per second The electrodes are saucer shaped silver plated and have a diameter of 5 mm one electrode is firmly fixed close to the outer canthus of each eye by means of sellotape and using Cambridge electrode jelly The earth electrode is fixed to the forehead in the same way The recording unit was calibrated by asking the subject to look alternately at two illuminated marks on the wall in front of him 20° apart The calibration was repeated after the irrigation and the mean of the two determinations used for the calculations The sensitivity of the recording apparatus was adjusted to give a pen deflection of about 1 mm per degree of eye movement The gain control could be adjusted in steps of 6 dB In addition the nystagmus was monitored visually using an oscilloscope

Procedure

The left ear only of these subjects was stimulated and as stated above only water of 44 C was used

Prior to commencing the caloric stimulation examination for resting spontaneous nystagmus was performed using the oscilloscope In each case three positions were used (1) In the sitting position with head erect and eyes closed (2) supine with head unrotated and unflexed and with the eyes closed (3) as for (2) but with the eyes open and fixating on the point on the ceiling in straight ahead line 140 cm distant from the subject's eyes The subject's head was then raised to give the slight head flexion necessary to place the lateral semicircular canal in the vertical position The left lateral semicircular canal was then stimulated by irrigating the left external acoustic meatus with the water 44°C for 40 seconds Fitzgerald & Hallpike 1942) According to the experimental set determined

TABLE 1 Sequence of caloric tests *Test condition I—eyes closed no mental arithmetic Test condition II—eyes open mental arithmetic Test condition III—eyes closed mental arithmetic*

	Subjects					
	A	B	C	D	E	F
Test condition order	I	II	III	I	II	III
	II	III	II	III	I	I
	III	I	I	II	III	II

METHOD

Experimental Design

In attempting to assess the influence of mental activity and visual fixation three test conditions were employed:

Test condition I

Absence of visual fixation and reduction of mental activity. The subjects were here tested in a dark room with the eyes closed lightly and were instructed to "just relax".

Test condition II

Presence of visual fixation with mental activity, here the subject was tested in a dark room, but with the eyes open and the gaze fixated on a 1 cm diameter light at a distance of 140 cm from the subject's eyes. During the test the subject was required to perform a serial-7 subtraction

Test condition III

Mental activity but without visual fixation Here the subject was tested in a dark room with the eyes closed lightly. During the test he was required to perform a serial-7 subtraction

To avoid any "carry-over" effect, between test condition II and III with respect to the serial-7 subtractions, the arithmetic was commenced at a value of "493" for test condition II and "595" for test condition III It was decided to test each subject under each of the three test conditions Since there are three test conditions, then the number of permutations that exists is 3!, i e, six possible sequences These are shown in Table 1

Use of all permutations of this particular combination of three test conditions is necessary to eliminate both order and "carry-over" (sequence) effects Order effects undoubtedly do exist with respect to responses to caloric stimulation, since this is formally equivalent to the phenomenon of response decline (equals habituation) "Carry-over" effects may also exist

Subjects

To have at least one subject for each testing sequence, six normal subjects were employed for this study Three of these were males and three females, with ages ranging from 24–31 years Clinically, they all had normal hearing and vision There was no history of vertigo or head injury and none had taken drugs or alcohol for at least three days prior to the tests All six subjects were otoscopically normal and any wax had been removed from the external acoustic meatus Equilibrium examination and examination for both spontaneous and positional nystagmus were done on each subject. The results were normal In the case of the women, the test was performed on the same day of the menstrual cycle

TABLE 2 *The median values of the indices of caloric-induced nystagmic response*

Test condition	Duration of nystagmus	Maximum velocity sl phase	Velocity 1 min deg /sec	Total number beats	Maximum number beats	Ratio beats duration	Total amplit 10 sec	Mean amplit 10 sec
I	134	22 1	15 9	77	12	0 52	46	3 2
II	0	0	0	0	0	0	0	0
III	165	27 7	20 9	101	15	0 65	93	6 0

The median values for each of these measures, 1 to 8 (except the last one), were calculated and they are shown in Table 2 The subjective estimate of the nystagmic recording regularity was performed by three observers, two were otorhinolaryngologists but the third one was an audiology assistant with considerable amount of experience in reading nystagmic recordings They were asked to classify each of the three recordings of each subject into one of two categories of nystagmic response but knew neither the identity of the recordings nor the irrigation sequence

The criteria for nystagmic response regularity were as follows

(*a*) *Regular or almost regular nystagmus* The successive recorded nystagmic beats are regular and distinct with respect to their frequency and amplitude

(*b*) *Irregular nystagmus* Here the regular nystagmus intervals last short and are replaced by longer periods of either distorted nystagmus recording or nystagmus-free intervals

The recorded nystagmic response that could not be classified into either of these categories was rated as intermediate nystagmus These results of rating are shown in Table 3

DISCUSSION

Inspection of Table 2 indicates that the rank order for the median values for each of the indices of nystagmic response is the same with each index, i.e. greatest response with test condition III and least response with test condition II

The results indicate that, of the three test conditions used, the greatest response was achieved by having the eyes closed and obtaining mental activity on the part of the subject, in this particular case by doing silent mental arithmetic, and the least recorded response is achieved by having the person fixate with the eyes open It is noted that, as Table 2 shows, the median response for each of the indices of nystagmic response for test condition II is zero It does not mean that there is no nystagmic response whatsoever from this condition, merely that none was recorded Experience has shown that with the eyes open, nystagmus recorded electro-oculo-

in Table 1 the subject had the eyes open or closed and mental arithmetic was or was not performed The recording paper was continued running until no nystagmus was recorded After an interval of 5 minutes (inter irrigation interval discussed by Lorente de Nó, 1935, Fitzgerald & Hallpike 1942, Jongkees, 1949, Cawthorne & Cobb, 1954) the second caloric test was performed under the appropriate conditions of the sequence, and then after another 5 minutes the third caloric test was given under the appropriate test conditions All tests were performed at the same time of day, by the same person and in the same physical environment

Analysis

Each nystagmus record was analysed with respect to the following indices of response [1]

1 Duration of nystagmus in seconds This was commenced at the start of the irrigation to the last detectable beat (see Barany, 1906, Van Egmond *et al*, 1949, Fitzgerald & Hallpike, 1942, Henriksson, 1956, Aschan *et al*, 1956)

2 Maximum velocity of the slow phase of nystagmus in degrees per second (see Dohlman, 1925, Hallpike & Hood, 1953, Van Egmond & Tolk, 1954, Henriksson, 1956, Aschan *et al*, 1956) In calculating this index due attention was paid to, and allowance made for, the fluctuating changes in velocity of the slow phase of nystagmus during the slow-swinging low frequency eye movements of Aschan *et al* (1956) (the autogenous eye wandering movements of Wendt, 1951) The velocity of the slow phase would certainly have been erroneously enhanced in the calculation if the directions of both the slow phase of a nystagmic beat and the slow-swinging eye movement had coincided

3 Velocity of the slow phase in degrees per second at 1 minute after the onset of the irrigation

4 Total number of beats during the period from 1 minute after the onset of the irrigation to the last detectable nystagmic beat

5 Maximum number of beats over a 10 seconds period centred around one minute after the onset of the irrigation

6 Ratio between total number of beats and duration in seconds

7 Total amplitude over a 10 second period centred around 1 minute after the onset of irrigation

8 Mean amplitude of this response for a 10 second period centred around 1 minute from the beginning of the irrigation

9 A subjective estimate of the regularity of the caloric induced nystagmic recording

[1] The latency has not been used as an index of nystagmic response because many authors are of the opinion that it is directly dependant on the structure of the temporal bone and does not reflect the physiological state of the labyrinth (Fitzgerald & Hallpike 1942, Jongkees, 1949, Cawthorne & Cobb 1954)

TABLE 2 *The median values of the indices of caloric induced nystagmic response*

Test condition	Duration of nystagmus	Maximum velocity sl phase	Velocity 1 min deg /sec	Total number beats	Maximum number beats	Ratio beats duration	Total amplit 10 sec	Mean amplit 10 sec
I	134	22 1	15 9	77	12	0 52	46	3 2
II	0	0	0	0	0	0	0	0
III	165	27 7	20 9	101	15	0 63	93	6 0

The median values for each of these measures, 1 to 8 (except the last one), were calculated and they are shown in Table 2. The subjective estimate of the nystagmic recording regularity was performed by three observers, two were otorhinolaryngologists but the third one was an audiology assistant with considerable amount of experience in reading nystagmic recordings They were asked to classify each of the three recordings of each subject into one of two categories of nystagmic response but knew neither the identity of the recordings nor the irrigation sequence

The criteria for nystagmic response regularity were as follows:

(a) Regular or almost regular nystagmus The successive recorded nystagmic beats are regular and distinct with respect to their frequency and amplitude

(b) Irregular nystagmus Here the regular nystagmus intervals last short and are replaced by longer periods of either distorted nystagmus recording or nystagmus-free intervals

The recorded nystagmic response that could not be classified into either of these categories was rated as intermediate nystagmus These results of rating are shown in Table 3

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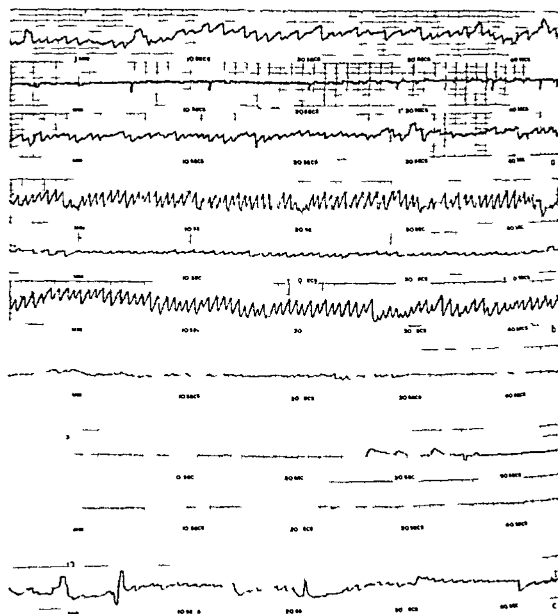
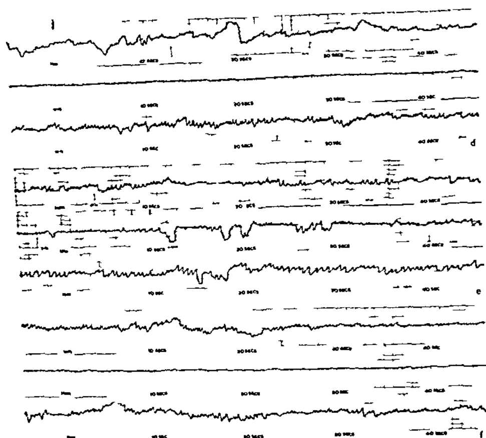


Fig. 1. Sample of caloric electronystagmogram for each of the three tests for each subject. For each subject the order of nystagmic response recording is from above downward: test condition I, test condition II and test condition III. The vertical lines separate intervals of 1 sec. The time denotes the duration after the onset of irrigation.
Fig. 1a Subject A. Fig. 1b Subject B. Fig. 1c Subject C. Fig. 1d Subject D. Fig. 1e Subject E. Fig. 1f Subject F.

graphically may be minimal or absent when it can be detected subjectively by the observer by direct inspection of the eyes. Although the median response is zero, some of the subjects did show a recorded nystagmic response (Fig. 1f, Fig. 1e). The absence of electro-oculographically recorded nystagmus (Fig. 1a, Fig. 1c, Fig. 1d) or when the recorded nystagmus is of insufficient magnitude to enable calculating various indices of



response in test condition II (Fig. 1 f) could be explained if we regard the visual fixation as a more dominant factor than the mental arithmetic. The instruction for performing continuous division with a constant divisor was given to the subjects in both test condition II and III and it was the influence of visual fixation that contributed in obtaining the least response with test condition II. The same has been observed by many other authors. Dodge (1923) found the reduced nystagmic response in repeated rotatory stimulation was due to increased visual dominance. In order to avoid this Wendt (1951), Aschan *et al.* (1956), Jongkees (1960), Hinchcliffe (1962) and many others prefer having the eyes closed during testing the vestibular labyrinth. As stated by Aschan *et al.* (1956) the nystagmic duration in equal in try the same applies to the velocity of the slow phase of nystagmus after rotatory stimuli could be even 30% longer with the eyes closed than when Frenzel glasses are worn. In a recent report from Mayo Clinic Mahoney *et al.* (19[illegible]) gave evidence that in normal subjects the amplitude and duration of caloric induced nystagmus (modified Kobrak's minimal test) are increased and the frequency decreased progressively with increasing interference with fixation. The same observation reported Henriksson

TABLE 3 *A subjective estimate of the regularity of caloric-induced nystagmic response recordings by two otorhinolaryngologists and an audiology assistant* *

The magnitude of the recorded nystagmic response in test condition II allowed evaluation of the indices of response only in two subjects In the other four subjects the magnitude of the recorded nystagmic response was not sufficient for evaluation of the indices of response

Observer		Test cond I			Test cond * II			Test cond III		
		Reg	Inter	Irreg	Reg	Inter	Irreg	Reg	Inter	Irreg
Orl	1	3	1	2	1	1		4	2	
Orl	2	3		3	1		1	2	4	
Audiology asst		2	2	2	1	1		3	3	

(1956) and Stahle (1958), i e , the amplitude and maximum velocity of the slow phase are reduced and sometimes even abolished if visual fixation occurs Even in darkness, Stahle (1958) and Hamersma (1957) reported longer duration of nystagmus by having the eyes closed than with the eyes open

Recently, Collins *et al* (1962) investigated the influence of varied visual fixation distance upon the caloric-induced nystagmus in normal subjects They obtained shorter duration of nystagmic response at a fixation distance 1 63 cm (a marker on the ceiling) than the 30 5 cm (a marker directly overhead) from the subject's eyes In both instances the eyes were open and mental arithmetic performed Two subjects in their pilot studies did not give apparent response, also one out of eight tested subjects (with no previous caloric testings) showed no observable reaction on the ceiling marker fixation It should be noted that they did not record the nystagmus but measured its duration with a stop watch and "for most subjects, the nystagmus produced under the illumination and fixation conditions, though detectable by direct observation was not of sufficient magnitude to be reliably scored" The visual fixation distance in test condition II is 23 cm shorter than the one used by Collins *et al* However, Mahoney *et al* (1957) showed that the recorded nystagmus response with visual fixation distance 30 cm from the eyes is also of smaller magnitude than the one obtained without fixation and having the eyes open As reported earlier by the author (Sokolovski, 1963) the least nystagmic response was recorded when the visual fixation distance was 2 m and the postrotatory stimulus was very strong indeed It appears that the visual fixation *per se* exerts a dominant influence and reduces the magnitude of the nystagmic response

The results of test condition III (Table 2) indicate an improvement of all indices of nystagmic response when the subject performed mental arithmetic with eyes closed The difference in the results between test condition I and III appears to be due to the applied mental arithmetic in the latter *condition* Here, the greater amplitude of the nystagmic beats

enables calculation of all indices of response in contrast to test condition II when testing was done with visual fixation. Mahoney *et al.* (1957) varied the state of alertness by giving the subjects arithmetic and spelling problems and obtained consistent facilitation of caloric nystagmic response. The occasional dysrhythmia of caloric-induced nystagmus which appears in normal subjets was converted to rhythmic nystagmus by varying the state of alertness with mental activity. It can be seen from Table 3 that the nystagmic response becomes less irregular in test condition III than in the other two conditions. McLay (1962) applied a mental activity in form of reply to a speech audiogram list on the part of the patient throughout caloric testing. The favourable effect of mental activity regarding the nystagmic response has also been shown in rotatory stimulation by Griffith, 1920; Mowrer, 1934; Wendt, 1951; Guedry & Lauver, 1961; Sokolovski, 1963.

It should be noted (Table 2) that this experiment design only catered for the degree of caloric-induced nystagmic response and did not take in the questions of variability. It is quite possible, though we think unlikely, that although the maximum response is achieved by abolishing optic fixation and performing mental arithmetic, that the variance may be as much if not more with this condition than with the other conditions. However, investigations by Collins (1962), Collins *et al.* (1961, 1962) and Collins & Guedry (1962) have indicated that the variability may be less. They all found the continuous silent mental arithmetic improving the duration and velocity of the slow phase of nystagmus. However, they also found that the subject may relax more towards the end of the caloric testing than in the beginning and during this reverie stage the vestibular reaction could be influenced by arousal effects. It can be noticed (Fig. 1 *c*, Fig. 1 *d*, Fig. 1 *e*, test condition I) that at any stage throughout the caloric testing there might be periods when no nystagmic response is recorded or the recorded nystagmic response is of small amplitude. Such dysrhythmia, as stated by Aschan *et al.* (1956), could be due 'either to suspected cerebral lesions or too short a time interval between consecutive irrigations' whereas Stahle (1958) thought it indicated vestibular dysfunction. However, Lidvall (1961) reported such irregularities in normal subjects as well. [illegible]

[illegible] calculating some indices of response (the velocity of the slow phase for example). Inspection of Fig. 1 *c*, Fig. 1 *d*, Fig. 1 *e* shows clearly the existence of intra subject variability in caloric testing and that could be controlled to some extent by abolishing the visual fixation and obtaining mental activity on the part of the subject. It appears that the occasional intra subject variability Fig. 1 *c*, Fig. 1 *f* (test condition III) is due to discontinuing mental activity on the part of the subject, i.e., alternation in the mental set up of relaxation and mental activity with varied intermediate stages. (Of course, apart from the differences in the thickness

of tympanic membranes and anatomical structure of temporal bones the different effects of various mental tasks will account for the inter subject variability) The mental effort must exist all the time and its degree should be high enough to provide constant continuous alertness The mental tasks vary in their effectiveness in achieving this requirement (Collins 1962 Sokolovski 1963) It appears that our main duty is to keep every subject alerted throughout the test to his alertness level and not allow this to fall off to the point where the central inhibition would take over and suppress the nystagmic response At present the mental arithmetic has been found the best for alerting the subject Improvements in control of the state of alertness could add more towards a reliable nystagmic response

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ZUSAMMENFASSUNG

Das linke Ohr wurde bei 6 normalen Personen mit 44°C heissem Wasser gespült und der Nystagmus elektrookulographisch registriert Mit drei Untersuchungszuständen wurde gearbeitet Zustand I ohne visuelle Fixation aber mit verminderter geistiger Aktivität Zustand II wenn sowohl visuelle Fixation als auch geistige Aktivität vorhanden waren Zustand III wenn geistige Aktivität herrschte aber visuelle Fixation abwesend war Bei Anwendung von 5 Nystagmusindexen (bei kalorischer Reizung) kam ein übereinstimmender stärkerer Nystagmus für Untersuchungszustand III vor Dieser Untersuchungszustand ergab Berichte die seltener als unregelmässig angesehen wurden als die Berichte für Untersuchungszustand I Die nystagmische Dysrhythmie kommt noch im Untersuchungszustand III vor

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EPISTAXIS TREATED WITH EPSILON-AMINO *n* CAPROIC ACID

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The fibrinolytic activity in nasal and in circulating venous blood as well as the activator content in the inferior concha were assayed and determined in patients with nose bleeding from this area. A considerable content of plasmin in the nasal blood as well as a high activator in the mucosa and the inferior concha was found. Generalized fibrinolysis could not be demonstrated in the circulating venous blood. Five patients with diffuse capillary incoagulable nose bleeding from the inferior concha were given initially 100 ml of a 6 per cent solution of epsilon amino-*n*-caproic acid resulting in complete hemostasis a few minutes after the infusion was terminated. In the case of recurrence 6 g epsilon amino-*n*-caproic acid was given by mouth at four hours intervals. No immediate side effects were noted.

INTRODUCTION

Yoshohisa *et al.* (1959) reported the presence of a considerable fibrinolytic activity (FA) in extractions from the mucosal surfaces of the nasal passages and the sinus maxillaris as well as the cartilaginous membrane coating the pharyngeal tonsils. This activity was found in the mitochondria fraction.

They also showed that the FA was completely inhibited by the addition of epsilon amino-*n*-caproic acid (e ACA).

At the Department of Otology of Kommunehospitalet, Copenhagen, we have reproduced this study and demonstrated a tissue activator content in biopsy specimens from the inferior conchae corresponding with the activity found in the uterus and the lungs, which are the two organs of the body so far known to have the highest content of plasminogen activity (Albrechtsen 1959).

In addition five patients with acute nose bleeding were treated with e-ACA in the assumption that the plasminogen being adsorbed to fibrin formed for hemostatic purposes is activated into plasmin in the presence

Supported by the Scientific Secretariat of Kommunehospitalet, Copenhagen.
This paper was presented at the meeting of the Danish Otolaryngologic Society, November 1962.

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TABLE 1 *The patients' sex, age, blood pressure and the origin of bleeding*
i c indicates inferior concha(e)

Case No	Sex	Age (yrs)	Site of bleeding	Blood pressure
1	Male	67	Left i c	200/110
2	Female	86	Right i c	160/90
3	Female	86	Both i c	180/100
4	Female	83	Both i c	165/105
5	Female	57	Both i c	190/100

Tissue activator determination

Biopsies were taken from the inferior concha by means of Hartmann's forceps without using local anesthesia 1 g of the tissue was promptly homogenized extracted three times for one hour in a 2 molar potassium thiocyanate solution centrifuged, and 0 03 ml was put on unheated fibrin plates and incubated for 24 hours at 37°C The figures presented again are averages of five plates

For the bovine plates we used Fibrinogene Bovin from Poviet Producenten N V Amsterdam, and of thrombin Topostasine from Roche was applied

e ACA initially was given as a 6 per cent solution A total of 100 ml was administered intravenously over ten to fifteen minutes, followed in the case of recurrence only, by 6 g orally every four hours Table 2 illustrated the duration of the treatment and the total dosages of e ACA

By heating the plates to 85°C for 45 minutes (Lassen, 1953) before the application of the extraction, the plasminogen which is always present together with fibrinogen is destroyed As a consequence fibrinolysis on the heated plate indicates the content of plasmin in the extraction, while fibrinolysis on unheated plates gives a relative index for the activator and plasmin contents

MATERIAL

The five patients who were treated with e-ACA arrived at the Department with profuse generalized capillary bleeding from the inferior concha The nasal blood in all cases was incoagulable In all five patients the bleeding started spontaneously or following minor exercise in three after getting out of their beds in the morning of the day of arrival, in one patient after getting up from a chair, in another while sitting in a chair reading a book Only one of the patients (No 5) had experienced nose bleeding previously having had nine months earlier a similar though milder episode which ceased after pinching the nose for a few minutes

As depicted in Table 1, only one patient was male In three of the

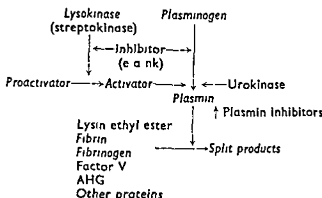


Fig 1 The fibrinolytic system (Astrup, 1956)

of the tissue activator released by the injured nasal mucosa Accordingly, the fibrin will be broken down and hemostasis compromised in the area of the lesion

In the literature we have found three cases of nose bleeding treated with e-ACA with prompt effect (Fletcher, Alkjærsig & Sherry, 1962, Nilsson Bjorkman & Andersson, 1961, Olow, 1962) The nose bleeding in these patients was a feature in other hemorrhagic disorders

In the process of fibrinolysis, fibrin is broken down by plasmin into polypeptides, peptides, peptones and other micromolecular compounds (Fletcher, Alkjærsig & Sherry, 1962) This enzyme under normal conditions is present in the circulating blood as the inactive precursor plasminogen According to Astrup (1956) this is a globulin with a pronounced affinity to fibrin, to which it is adsorbed, thereby facilitating the breakdown Plasmin breaks down not only fibrin, but also, at higher plasma concentrations, certain coagulation factors, viz fibrinogen, factor V (pro-accelerin) and factor VIII (antihaemophiliglobulin) and plasminogen+pro-activators (Niewiarowski & Latallo, 1957, Olow, 1962), cf Fig 1, and the resulting coagulation deficiency increases the bleeding tendency

Plasminogen is convertible into plasmin by the release of activators in the tissue strongly bound to the tissue proteins and in the circulating blood by kinase activation of the pro-activators (Fig 1)

METHOD

Blood-samples

Citrated blood from the nasal excretion was collected immediately after the patients' arrival as well as venous blood from the plica cubiti (without application of tourniquet) The samples were centrifuged at once, placed in refrigerator at 0°C, and some minutes later, 0 03 ml of whole plasma was dropped in three places on bovine fibrin plates at 37°C for 24 hours The presented figures represent averages of five plates

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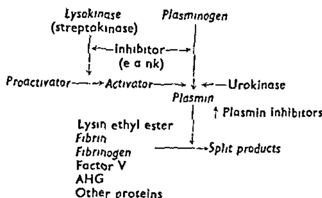


FIG 1 The fibrinolytic system (Astrup, 1956)

of the tissue activator released by the injured nasal mucosa Accordingly, the fibrin will be broken down and hemostasis compromised in the area of the lesion

In the literature we have found three cases of nose bleeding treated with e-ACA with prompt effect (Fletcher, Alkjærsig & Sherry, 1962, Nilsson Björkman & Andersson, 1961, Olow, 1962) The nose bleeding in these patients was a feature in other hemorrhagic disorders

In the process of fibrinolysis, fibrin is broken down by plasmin into polypeptides, peptides, peptones and other micromolecular compounds (Fletcher, Alkjærsig & Sherry, 1962) This enzyme under normal conditions is present in the circulating blood as the inactive precursor plasminogen According to Astrup (1956) this is a globulin with a pronounced affinity to fibrin, to which it is adsorbed, thereby facilitating the breakdown Plasmin breaks down not only fibrin, but also, at higher plasma concentrations, certain coagulation factors, viz fibrinogen, factor V (pro-accelerin) and factor VIII (antihaemophiliglobulin) and plasminogen + pro-activators (Niewiarowski & Latallo, 1957, Olow, 1962), cf Fig 1, and the resulting coagulation deficiency increases the bleeding tendency

Plasminogen is convertible into plasmin by the release of activators in the tissue strongly bound to the tissue proteins and in the circulating blood by kinase activation of the pro-activators (Fig 1)

METHOD

Blood-samples

Citrated blood from the nasal excretion was collected immediately after the patients' arrival as well as venous blood from the plica cubiti (without application of tourniquet) The samples were centrifuged at once, placed in refrigerator at 0°C, and some minutes later, 0 03 ml of whole plasma was dropped in three places on bovine fibrin plates at 37°C for 24 hours The presented figures represent averages of five plates

TABLE 1 *The patients sex age blood pressure and the origin of bleeding*

i.c indicates inferior concha(e)

Case No	Sex	Age (yrs)	Site of bleeding	Blood pressure
1	Male	67	Left i.c	200/110
2	Female	86	Right i c	160/90
3	Female	86	Both i c	180/100
4	Female	83	Both i c	165/105
5	Female	57	Both i c	190/100

Tissue activator determination

Biopsies were taken from the inferior concha by means of Hartmann s forceps without using local anesthesia 1 g of the tissue was promptly homogenized extracted three times for one hour in a 2 molar potassium thiocyanate solution centrifuged and 0 03 ml was put on unheated fibrin plates and incubated for 24 hours at 37°C The figures presented again are averages of five plates

For the bovine plates we used Fibrinogene Bovin from Poviet Producten N V Amsterdam and of thrombin Topostasine from Roche was applied

e ACA initially was given as a 6 per cent solution A total of 100 ml was administered intravenously over ten to fifteen minutes followed in the case of recurrence only by 6 g orally every four hours Table 2 illustrated the duration of the treatment and the total dosages of e ACA

By heating the plates to 85°C for 45 minutes (Lassen 1953) before the application of the extraction the plasminogen which is always present together with fibrinogen is destroyed As a consequence fibrinolysis on the heated plate indicates the *content* of plasmin in the extraction while fibrinolysis on unheated plates gives a relative index for the *activator and* plasmin contents

MATERIAL

The five patients who were treated with e ACA arrived at *the* Department with profuse *generalized* capillary bleeding from the inferior conchae The *nasal blood* in all cases was incoagulable In all five patients the bleeding started spontaneously or following minor exercise in three after getting out of their *beds* in the morning of the day of arrival in one patient after getting up from a chair in another while sitting in a chair reading a book Only one of the patients (No) had experienced nose bleeding previously having had nine months earlier a similar though milder episode which *ceased after* pinching the nose for a few minutes

As depicted in Table 1 only one patient was male In three of the

TABLE 2. *The e-ACA administration, duration treatment, total dosage and side effects.*

Case No	Initial dosage of 6 % i v	Days of treatment	Total dosage in g	Side effects
1	100	(1)	6	None
2	100	1	42	None
3	100	1	30	None
4	100	4	96	None
5	100	8	201	None

patients the bleeding originated in both inferior conchae The blood pressure in all of the patients was slightly to moderately increased The median age was 75 years. In no case the blood samples collected immediately after arrival at the ward—prior to infusion of e-ACA—revealed abnormalities in bleeding or coagulation time, nor in prothrombin time or platelet counts

RESULTS

Table 2 shows the FA determined as described above The activity was assayed on heated and unheated bovin fibrin plates, in nasal as well as in the circulating venous blood. The normal activity in venous blood determined by the area of lysis varies from 0 to 70 mm² on unheated plates (*Andersson & Nilsson, 1961*). *In patient No* 3 the determination was unsuccessful

In four patients the FA was found to be considerably higher in the nasal blood than in the circulating venous blood The interval between the sampling of the nasal and the venous blood was a few minutes at the most Accordingly, it must be assumed that the activity found in the nasal blood had been generated by local fibrinolysis at the site of the bleeding

A simultaneous determination of the FA in the circulating venous blood showed, as already mentioned, no evidence of generalized fibrinolysis (Table 3) A demonstration of normal activity in the circulating venous blood does not exclude, however, that a considerable fibrinolytic activator activity might have taken place, as increases of very short duration are seen, indicating the labile nature of the kinases present in the *circulating* blood in contrast to the tissue activator which is strongly bound to the tissue protein and stable even at temperatures up to 60° for 30 minutes

In all five patients the nose bleeding ceased immediately after termination of the infusion of e-ACA, which lasted for some ten minutes *No side* effects were noted in connection with the infusion

As will be seen from Table 2, FA in the first two cases was determined on unheated plates on extractions from the inferior concha taken immedi-

TABLE 3 *The determinated fibrinolytic activity on heated and unheated bovine fibrine plates in the nasal blood circulating venous blood and in the tissue of the inferior turbinate*

Plates	Blood flow from the nose		Circulating venous blood		Tissue of inf turbinate unheated
	heated	unheated	heated	unheated	
Case 1	132	[illegible]	12	50	328
2	102	181	16	90	[illegible]
3	Failed	Failed	Failed	0	
4	182	[illegible]	Not determined		Not determined
	115	205	[illegible]	55	

ately before the infusion of ε-ACA further that they revealed a considerable activity the areas of lysis being 328 and 296 mm² respectively In addition we determined the FA in biopsies from the inferior concha in five younger patients presenting no rhinological abnormalities or pathological laboratory findings having been admitted to the Department for other reasons (tonsillectomy) The mean value of the tissue activator content determined in five plates each was 285 mm² lysis on unheated plates Even though the material includes only seven determinations of the tissue activator content in the inferior concha it seems reasonable to conclude from the results obtained that the mucosa of the inferior concha contains considerable amounts of tissue activator This observation has not been reported previously Lesions of the mucosa of the inferior concha e g caused by a ruptured arteriosclerotic vessel can release tissue activators resulting in generalized bleeding within the concha

CONCLUSION

In patients with epistaxis from the inferior concha obviously representing diffuse capillary bleeding of incoagulable blood it is possible and likely that the bleeding is maintained by a plasminogen activator released from the tissue as the mucosa of the inferior concha has been found under normal conditions to contain a large amount of plasminogen activators

Injury to the tissue of the inferior concha as caused by the rupture of an arteriosclerotic vessel will release these activators resulting in the conversion of plasminogen into plasmin As a consequence the action of some of the normal coagulation factors of the blood is prevented On the other hand the antiplasmin effect of the blood under normal conditions is so great and higher than the total potential plasmin activity that it seems more reasonable to assume that the bleeding is maintained by plasmin

TABLE 2 *The e-ACA administration, duration treatment, total dosage and side effects.*

Case No	Initial dosage of 6 % i v	Days of treatment	Total dosage in g	Side effects
1	100	(1)	6	None
2	100	1	42	None
3	100	1	30	None
4	100	1	96	None
5	100	8	204	None

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breakdown of the fibrin formed—possibly in the very moment of its formation (Niewiarowski & Latallo 1957). This assumption is supported by the frequent finding of high activator activity which by activation of fibrin bound plasminogen uninfluenced by the anti plasmin effect of the blood may give rise to localized fibrinolysis and bleeding.

Accordingly it seems logical to treat these bleeding disorders with a plasminogen activator inhibitor like e-ACA. This agent can be used as a test of fibrinolytic bleeding in so far as after intravenous administration of 1 g e-ACA per 10 kg body weight there will be a striking effect or none at all. The use of e-ACA for diagnostic purposes in acute hemorrhagic disorders is hazardless and will not obscure other aetiological conditions (Nilsson, Björkman & Andersson 1961). If the bleeding ceases after administration of 6 g of e-ACA intravenously it may be concluded that it has been caused by fibrinolysis.

Spink in 1961 revealed that the physiological effect of e-ACA is not only antifibrinolytic but may also be of an antianaphylactic and vegetative nature (Yoshohisa *et al.* 1959). Further it has been demonstrated that e-ACA has a *beneficial effect on certain forms of hemophilia (Reid et al.* 1964) and on some thrombocytic disorders (Salmon 1961). One should not, however, rest satisfied with the diagnosis localized fibrinolysis in the case of a favorable response to e-ACA but be careful to exclude possible other causes by referring the patients to continued hematological investigations.

*Clinical reports seem to indicate that e-ACA increases the risk of thr*omboses especially in long term therapy of elderly arteriosclerotic or thrombosis suspected patients (Naeye 1962, Olow 1962, Yasuo *et al.* (1962). If however the decision is made to institute a prolonged treatment with e-ACA it should be combined with anticoagulantia or the more recent drug Trasylol which is a potent plasminogen activator inhibitor as well as a direct plasmin inhibitor and has thromboplastic effect (Amris 1964).

The administration of a plasminogen activator inhibitor in diffuse capillary incoagulable bleeding from the inferior concha is recommended.

ZUSAMMENFASSUNG

Die fibrinolytische Aktivität im Nasenblut und im zirkulierenden venösen Blut sowie der Aktivatorgehalt der Conchae inferiores sind untersucht und die Grösse derselben bei Patienten mit Nasenblutung des Conchae inferiores Bereiches *bestimmt* worden. Im Nasenblut wurden beträchtliche Mengen Plasmin gefunden und in der Schleimhaut der Concha inferior ein hoher Aktivatorgehalt. Im zirkulierenden venösen Blut konnte dabei keine generelle Fibrinolyse festgestellt werden. Fünf Patienten *mit diffuser kapillärer, nicht koagulierbarer* Nasenblutung der Conchae inferiores erhielten zur Einleitung 100 ml einer 6 prozentigen Epsilon-Amino-n-Kapronsäure-Lösung. Wenige Minuten nach dem Abschluss der Infusion erreichte man vollständige Hämostase. Bei Rückfall behandelte man die Patienten mit Eingabe von 6 g Epsilon-*n*-Amino-Kapronsäure jede vierte Stunde. Es wurden keine unmittelbaren Beiwirkungen beobachtet.

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FACTORS AFFECTING VESTIBULAR NYSTAGMUS IN CORIOLIS STIMULATION

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The influence of certain factors on the electronystagmographic (ENG) recordings of vertical vestibular nystagmus induced by Coriolis stimulation is demonstrated. The factors studied are four. Condition A is eyes open in a state of reverie Condition B is eyes open in a state of alertness using mental arithmetic problems. Condition C is eyes closed in a state of reverie and Condition D is eyes closed in a state of alertness using mental arithmetic problems

The results demonstrate the influence of these four factors on the decay function and the sensitivity of nystagmic responses to Coriolis stimulation A discussion of the preferred condition for recording vertical nystagmus is presented with the admonition that in presenting nystagmic recordings as a result of rotation it is important to indicate the conditions and the environment to which a subject is exposed during nystagmic recordings

Throughout the literature there appears to be contrasting views in nystagmography as to the varying factors which influence nystagmus Electronystagmography was first proposed in 1922 by Schott (1922), which was the recording of cornea-retinal potentials The main advantage of this method was that the eyeball was never touched In 1955, Aschan applied it to clinical evaluations

According to Aschan *et al* (1956, 1957), the closing of the eyelids was recommended for recording vestibular nystagmus to rotary stimulations. Aschan (1957) claimed that the use of the Graybiel oculogyral illusion test (Graybiel & Hupp, 1946) lessened the slow phase of post-rotary nystagmus approximately one tenth of corresponding values measured with eyes closed Lansberg (1957), Stahle (1957), and Koike (1959) reported that the eyes being closed increased the nystagmic trace Rademaker & ter Braak (1948) demonstrated that with the eyes closed labyrinthine nystagmus occurred, but with eyes open no occurrence of nystagmus was recorded It appears that such recordings may have been taken in a lightened room which certainly would decrease eye movements due to visual fixation

However, many clinicians and researchers such as Preber (1957) and

Montandon (1954) have highly recommended that the eyes be kept open in a darkened area for recording nystagmus to rotary stimulation. Recently, another factor added to the one of eyes open in the dark was the state of alertness or mental activity. Collins (1962) and Naito *et al.* (1963) have both demonstrated the influence of an arousal state on the nystagmic output. Both used mental arithmetic to attain a high level of arousal in individuals whose nystagmic responses to rotary stimulations were being recorded.

Determination of the most advantageous conditions in which electronystagmograms are recorded is necessary to obtain accurate evaluations of the vestibulo-ocular reflex arc system. Certain essential conditions involved in nystagmography under rotary stimulation must be identified. The present study was undertaken to determine the most suitable conditions for recording nystagmus of human subjects to Coriolis stimulation, which was the test used in the Aeromedical Evaluation for Space Pilots (Cramer & Dowd 1963). The eye movements to be recorded in this study were vertical, not horizontal as most previously mentioned authors have recorded.

METHOD

Forty-five nonflying airmen were observed. Subjects were between the ages of seventeen and twenty-four years with 20.1 as the mean age. Requirements for each subject included: (1) history of auditory or vestibular impairments lacking; (2) apparently normal auditory canals and tympanic membranes; (3) absence of evidence of spontaneous, positional or abnormal gaze nystagmus on examination of eyes open and closed. The occurrence of motion sickness during the experiment was also disqualifying. Thirteen subjects were disqualified for reporting or showing motion sick symptoms. As a result thirty-two subjects completed all experimental conditions.

Four different conditions were used during this test. Each subject served under all four conditions, which were randomly assigned to each subject. [illegible]

[illegible] state of reverie (A), eyes open in an alert state (B), eyes closed in a state of reverie (C), and eyes closed in an alert state (D).

Before being tested a demonstration of the chair being *rotated and tilted* was given. Then each subject was seated in the USAFSAM biaxial stimulator with head positioned in a specially constructed headrest in order to lessen head movements. A *seat belt* was fastened across his thighs. Each subject was instructed *to refrain* from such activities as eye blinking, twitching, fixating on any *imaginary* horizon, moving eyebrows, and talking.

A calibration of *vertical eye movements* was recorded before and after testing. The subject was asked *to sweep* his eyes up and down between two markers spaced 18 *inches* vertically apart and placed 5 feet from the subject's head, *forming an* approximate 12 degrees eyeball displacement.

The light-proof room was *darkened*, *chair* tilted 30 degrees to the left

then rotated counterclockwise at 18 rpm, and the test commenced. The first tilt experienced was a pre-test trial tilt to acquaint the subject with the Coriolis sensation before proceeding to one of the four conditions. In the state of reverie, the subject was asked to relax and try not to concentrate on his position or movement. In the alert state the subject was presented with a mathematical problem which was a divisional one. The test consisted of the subject being rotated counterclockwise at 18 rpm while his head was 30 degrees from the vertical on the left side. After 1 minute of constant velocity at 18 rpm, the subject was tilted about the axis through the sternum to approximately 30 degrees from the vertical which required 3 seconds, after which the head was tilted on the right side. During this tilt (head position going from left to right) the subject was instructed to follow one of the four conditions previously mentioned.

Two minutes after each tilt the chair slowly decelerated to full stop, subject was returned to the vertical; room was lighted, and instructions were given for the next condition. The subject was observed for signs or symptoms of motion sickness (perspiring, pallor, epigastric awareness, compulsive swallowing, dizziness and nausea) after each tilt, and was questioned as to his sensations of movement. If he reported any discomfort leading to motion sickness, the test and the remaining conditions were not continued.

Electronystagmograms were taken on each subject. Five silver disc EEG electrodes were mounted around the eyes, two above the middle of the orbital frontal rim, two below the middle of the orbital ventral rim, and the indifferent electrode mounted on the forehead between the eyebrows. These electrodes were used to record vertical eye movements induced by the Coriolis stimulation. The electronystagmogram was preamplified by a Grass low-level d.c. pre-amplifier filtered at ½ amplitude at 15 cps, which passed to a Heiland 906B galvanometer recorder. Time constant of the entire system was 1.8 seconds. A tilt signal from a d.c. potentiometer was also recorded. Figure 1 demonstrates the electronystagmograms of two subjects and their responses to the varying conditions.

Recovery of the nystagmic response to stimulation was *approximated* by the negative exponential decay function

$$R_t = R_0 e^{-\beta t}$$

where t = seconds after cessation of the tilt stimulus, R_t = response at any time t, and R_0 = response at cessation of the tilt stimulus. The exponent β is the rate of decay or recovery of nystagmus to a Coriolis acceleration. From the dynamic characteristics and the maximum eye velocity the sensitivity of the system was computed to the function

$$\alpha S = \frac{R_0}{1 - e^{-3\beta}}$$

(Cf. Cramer & Dowd, 1963; Dowd, 1965.)

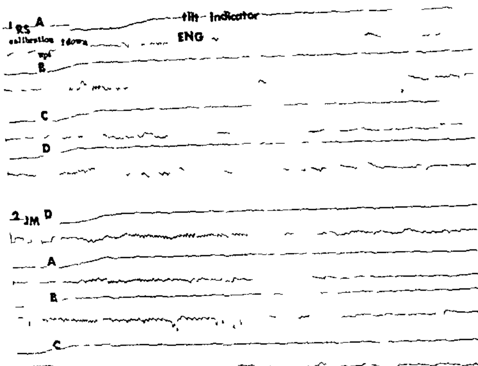


Fig. 1. Examples of the recorded vertical nystagmic responses (ENG) of two subjects demonstrating two of the four orders of presentation (1 and 2) of the four conditions (A to D). The conditions are: A = eyes open reverie, B = eyes open alert, C = eyes closed reverie, and D = eyes closed alert. Calibration signals of eyeball displacements of a 12° shift between upward and downward movements are presented prior to the first order condition of each subject. Blinking artefacts can be observed during both condition B traces by the sharp downward trace.

RESULTS

Thirteen subjects were eliminated from the results due to motion sickness. The responses of the remaining thirty-two subjects were analyzed on each of the four conditions using a Latin square design for the order of testing. The conditions were eyes open and closed in a state of reverie or alertness. A negative exponential decay function was fitted for each subject for each condition and exponents of the decay of nystagmus (β) were obtained. Also, sensitivity coefficients (αS) were calculated for each subject for each condition. These two variables were analyzed and the analyses of variance are given in Table 1.

Significant F's were obtained for the four different condition effects on both the decay functions and sensitivity coefficients (β and αS), which indicated that the difference in the four conditions tested resulted in significant modifications of the nystagmic responses to Coriolis stimulation. No

TABLE 1 *Analyses of variance*

Source	DF	M Sq	F	P
Decay function (β)				
Conditions	3	0 011722	20 80	<0 001
Square × Condition	21	0 000564		
Order	3	0 000740	0 92	NS
Square × Order	21	0 000805		
Subjects	31	0 001671		
Residual	48	0 000918		
Sensitivity (α S)				
Conditions	3	223 06	38 06	<0 001
Square × Condition	21	5 8608		
Order	3	11 466	2 43	NS
Square × Order	21	4 7112		
Subjects	31	17 105		
Residual	48	6 7778		

significance resulted from the order of presentation for both β and αS, which indicated that the order of the presentation of conditions did not affect nystagmic responses, nor display any practice effects

Table 2 presents the mean and the standard deviations for both variables β and αS for the four conditions For the exponent (β) of the decay of nystagmus, the eyes open alert (B) and eyes closed reverie (C) means were not different from each other at the 0 05 level but were different from the other two conditions (A and D) ($P<0$ 01) Eyes open reverie (A) and eyes closed alert (D) were significantly different from each other ($P<0$ 01)

The means of the alert conditions (B and D) did not differ at the 0 05 level for sensitivity coefficients (αS) These means, however, differed from the means of the reverie conditions (A and C), which also differed from each other ($P<0$ 01)

Examples of the recorded vertical nystagmic responses appear in Fig 1

TABLE 2 *Means and standard deviations* [a]

Conditions	β	αS
A Open, reverie	0 1177	5 01
B Open alert	0.1204	8 10
C Closed reverie	0 1195	3 22
D Closed alert	0 1012	8 87
Standard deviations[b]	0 0237	2 42

[a] Degrees of freedom = 21 This the standard deviation to be used in comparing these means but not for comparing these means with any other means

[b] N = 32

Two of the four orders of presentation (1 and 2) of the four conditions (A to D) are illustrated for two different subjects Note the difference between each condition as to the nystagmic traces These examples show that condition C (eyes closed reverie) produced the smallest trace while condition B (eyes open alert) and condition D (eyes closed alert) show the greatest nystagmic trace It may be noted that condition B produced blinks which interfered with an accurate nystagmic trace using this recording method

DISCUSSION

The primary purpose of this experiment was to determine the influence of certain factors (eyes open reverie eyes open alert eyes closed reverie and eyes closed alert) on the vertical vestibular nystagmus induced by Coriolis stimulation Research on the role of these factors has demonstrated their *influence* on *horizontal* vestibular nystagmus but no research has been reported on vertical vestibular nystagmus exposed to these factors

By inspection Fig 1 indicates that the mental state of reverie or alertness with eyes open or closed does modify the vertical *nystagmic recordings* to Coriolis stimulation The results of Tables 1 and 2 indicate the importance of a subject s mental state in recording vertical nystagmus Only the decay function exponents and coefficients of nystagmus were analyzed The *frequency* of nystagmus (number of beats per unit of time) was too variable to be considered of any significance to the results of these *conditions* on nystagmus This is in accord with Jongkees & Philipszoon (1963)

Since Mowrer (193[illegible], 1937) demonstrated the inhibitory effect of vision on vestibular response to rotation darkness was preferred and used for testing Darkness itself tends to produce a reverie state of mind Many times a response decline may result from reverie rather than from a true habituation factor or the involvement of a true central inhibiting process However in this particular stimulating *environment the Coriolis* stimulus created by tilting in the dark during rotation certainly does excite an individual It would be difficult to remain in a calm state during such a stressful stimulus (Dowd 196[illegible])

Condition A (eyes open reverie) displayed an active nystagmic trace A *different* result however appeared with condition C (eyes *closed reverie*) indicating that nystagmus was greatly inhibited by closed eyelids in a state of *reverie* Similar findings were reported by Mahoney *et al* (1957) for caloric horizontal nystagmus and by Naito *et al* (1963) for rotary horizontal nystagmus Regardless of the exciting Coriolis stimulus of pitch a strong nystagmus response during eyes closed reverie did not occur Condition D (eyes closed alert) however produced a sharp increment in nystagmus showing the affects of an alert state on *nystagmus* A conclusion can be drawn from these results *indicating* that it is essential to have the subject in an alert mental state in order to produce *a good* measurable nystagmic trace in recording nystagmus with eyes closed

Since the closing of eyelids does inhibit nystagmus as shown by Condition C in an environment of total darkness, eyes opened is preferred In comparing eyes open reverie (A) with eyes open alert (B), it was apparent that the alert state (B) does increase nystagmic sensitivity During this eyes open alert condition a blinking reflex accompanied mental arithmetic problem-solving, which interfered with the vertical nystagmic response traces In Fig 1, such blinking artefacts appear during condition B for both subjects It is interesting to note that mental arithmetic does influence this blinking reflex while recording vertical nystagmus Guedry & Montague (1961) found that blinking interfered with vertical nystagmic recordings while the subject was in a state of reverie It is interesting also, to note and observe from other reports (Preber, 1957, Montandon, 1954, Collins, 1962, and Collins & Poe, 1962) that blinking did not occur during horizontal nystagmic recordings while the subject was in an alert mental state It appears that vertical nystagmus does affect the blinking reflex which can be voluntarily controlled if the subject is instructed to refrain from blinking When a mental arithmetic problem has been presented to the subject, however, he loses this voluntary control of inhibiting blinking

Eyes open reverie (A) produced rather good measurable traces without any interfering artefacts such as blinking As a result, the most favorable and practical method of recording vertical vestibular nystagmus to Coriolis stimulation appears to be under condition A—eyes open reverie In recording horizontal vestibular nystagmus, however, condition B appears to be the best since blinking doesn't interfere with its recordings (Collins 1962)

In conclusion, nystagmus has been observed to be influenced by certain psychological factors as "attention" (Collins, 1962) and "excitement" (Dowd, 1965) It has been demonstrated that analeptic drugs affect nystagmic responses (Dowd, 1964) Like most sensory systems the modulating role of the cortex, limbic system, and brainstem reticular system appears to be responsible for the nystagmic output induced by some vestibular input In neonates, Pendleton & Paine (1961) found that "the absence of vestibular nystagmus under proper conditions seems one of the most sensitive signs in the newborn" when there is some "alteration of the state of consciousness" They found nystagmic modifications earlier than electroencephalographic tracings or respiratory rates and rhythms at the onset of sleep Collins & Posner (1963) found electronystagmography to be a more sensitive indicant of mental activity than EEG patterns

Thus, it is important when presenting nystagmic results to *rotation* to indicate the conditions and environment to which a subject was exposed during nystagmic recordings Factors such as eyelids open or closed, a reverie or alert state of mind, and the visual field (lighted or darkened area) have considerable influence on the decay function and the sensitivity of nystagmic responses to rotation

ACKNOWLEDGMENT

The author wishes to acknowledge and express his appreciation to Dr R L Cramer and E W Moore for their advice and assistance, to D B Helms and T L Colling for their excellent technical assistance, and to R C McNee for his contribution in data analysis

ZUSAMMENFASSUNG

Der Einfluss bestimmter Faktoren auf die elektronystagmographische (ENG) Registrierung des durch Coriolisreizung hervorgerufenen senkrechten Vestibularnystagmus wird aufgezeigt Vier experimentelle Bedingungen werden untersucht In Bedingung A befindet sich die Versuchsperson im Zustand der Entspannung und die Augen sind geöffnet In Bedingung B befindet sich die Versuchsperson im wachsamen Zustand der durch im Kopf gelöste arithmetische Aufgaben hervorgebracht ist und die Augen sind geöffnet In Bedingung C ist die Versuchsperson in einem Zustand der Entspannung mit geschlossenen Augen und in Bedingung D mit Augen geschlossen ist Wachsamkeit durch arithmetische Probleme gewährleistet

Die Ergebnisse zeigen den Einfluss dieser vier Bedingungen auf die funktionelle Form der Abnahme und die Empfindlichkeit der Nystagmusreaktion auf Coriolisreizung Die beste experimentelle Bedingung für die Registrierung des senkrechten Nystagmus wird diskutiert und es wird darauf hingewiesen dass bei der Beschreibung der Registrierung des durch die Rotation erzeugten Nystagmus die experimentellen Bedingungen und die Umgebungsverhältnisse mit angegeben werden müssen

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NON-EXPERIMENTAL AURAL PATHOLOGY IN SQUIRREL MONKEYS (SAIMIRI SCIUREUS) AND MARMOSETS

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In the marmoset, with the clusters of mastoid and apical pneumatic cells in wide communication to the central tympanic space, an undivided cavity is created. Simultaneous involvement of the entire area by infectious processes is bolstered by the lack of walling-off partitions. The tegmen is everywhere readily and frequently penetrated. From the apical cell group the spheno-occipital synchondrosis was predominantly seen invaded, with the consequence of an osteomyelitis of the cranial base. Frequency of otitis media advancing to lethal endocranial complications is in its portent equivalent to other generally listed causes of death as pulmonary, intestinal, parasitic ones. The inner ear is surrounded by pneumatic cells. In spite of being suspended in a similarly exposed situation it is less prone to react to infections. Suppurative processes of the middle ear when reaching the inner ear are mostly toned down to a sero-fibrinous one. The otic capsule was never seen penetrated by suppuration. Anatomical arrangement around cochlea and vestibulum results in their ready accessibility from all directions, a circumstance of considerable advantage in experimental work on the inner ear.

The establishment of Regional Primate Research Centers will enhance studies on these animals *per se* and establish them more firmly as the experimental animal closest to man. It becomes mandatory to care for their health and this carries with it the duty to study the pathological basis of their common ailments. In embarking on experiments (e.g. Seiden, 1958; Fujita & Elliott 1965) it is essential not to ignore factors that will make the use of this material futile for experimental purposes.

Sanderson (1957) pointed out the extraordinarily high mortality of squirrel monkeys. He suspected in their remarkable fragility some unknown basis that needs further study. On the other hand Carmichael & MacLean (1961) found Saimiri sciureus highly resistant to bacterial infections and

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noted that they readily withstood experiments requiring prolonged anesthesia and exposure of the brain. Benirschke & Richart (1963) had a high mortality when establishing and maintaining a breeding colony of marmosets. This problem arose from importation of infected specimens with the result that most of the marmosets perished soon after arrival. Greenstein, Doty & Lowy (1965) tabulated data on the morbidity and mortality of their colony. Sobel, Mondon & Means (1960) lost newly acquired pigmy marmosets due to infection causing both pulmonary diseases and diarrhea. Sanderson (1957) found that specimens of Oedipomidas oedipus die for no apparent reason.

The bibliography attached to the chapter by Berberich & Kelemen (1958) shows the scarcity of publications on ear diseases in primates. Eckstein & Zuckerman (1957) among their references listed items of tuberculosis in laboratory monkeys and Fiennes (1957) items on parasites and dysentery. Zuckerman (1962) mentioned that routine observations of diseases of which monkeys in the care of the Zoological Society of London succumbed began about 1830.

In a marmoset colony Levy & Artecona (1964) found as most common ailments upper respiratory infections, infestation with parasites and following dietary changes gastrointestinal disturbances. They explained that most of the diseases to which the animals are susceptible can be treated successfully. Benirschke & Richart (1960) observed spontaneous acute toxoplasmosis in a marmoset.

According to Sanderson squirrel monkeys (Saimiri) are found in seemingly endless groups often containing hundreds of members. He enumerated 4 species and 15 subspecies and mentioned considerable confusion as to just what is meant by the "common marmoset" with the Latin name Hapale jacchus constantly attached. According to Fiedler (1956) Saimiri, among them Saimiri sciureus, are placed in nearest relationship to Cebus, a genus where equal confusion as to systematics seems to exist.

Based on the classification of Simpson (1945), Table I shows the grouping of the monkeys in question.

Table I

Suborder Anthropoidea
  Family Cebidae
    Subfamily Aotinae
      Callicebus
    Subfamily Cebinae
      Saimiri
  Family Callithricidae (Hapalidae)
    Callithrix (Hapale, Marmosets)
    Leontocebus (Oedipomidas, Tamarin)

MATERIAL AND METHODS

The 24 animals serving as basis for these studies can be classified according to Table 1 Sixteen were females released for these studies by Dr Kurt Benirschke Professor of Pathology Dartmouth College, the remaining—without indications of their sex—originate from different sources

TABLE 2

Cebidae	
Callicebus Cupreus	2
Saimiri Sciureus	8
Callithricidae	
Hapale jacchus (Callithrix jacchus)	7
Oedipomidas oedipus	6
Tamarinus nigricollis	1
	24

From the cranial base a segment was dissected containing both ears After skinning from the external ear only the deepest portion remained The specimen was decalcified and embedded in celloidin At serial sectioning in the majority of the celloidin blocks a horizontal plane was chosen parallel with the general plane of the cranial base while in some instances the frontal plane was chosen The advantage obtained was to have both ears in the same section under the microscope the disadvantage was that both ears were sectioned in the same plane Hematoxylin eosin Heidenhain-Mallory staining and impregnation according to Gomori followed A number of mounted sections were left unstained to be studied in polarized light and under phase illumination No bacteriological study was attempted

Statistical evaluation will be omitted as the number of cases is too small to lend significant results To process larger numbers will always meet with obstacles because of the lengthy and laborious procedure of embedding temporal bones in celloidin

Anatomical Considerations

Before turning to the pathological findings some discussion of the ear anatomy in these animals is in order

Van Kampen's monograph (1905) on the middle ear of mammals is frequently quoted and served as a basis for later studies Van Kampen named Pohl (1818) as one of the first to describe the tympanic cavity in animals This was followed by the basic work of Hagenbach (1835) who described among monkeys gradual protruding of the inferior aspect of the temporal until Hapale jacchus shows the definite osseous bulla, and Hyrtl (1845)

noted that they readily withstood experiments requiring prolonged anesthesia and exposure of the brain Benirschke & Richart (1963) had a high mortality when establishing and maintaining a breeding colony of marmosets This problem arose from importation of infected specimens, with the result that most of the marmosets perished soon after arrival Greenstein, Doty & Lowy (1965) tabulated data on the morbidity and mortality of their colony Sobel, Mondon & Means (1960) lost newly acquired pigmy marmosets, due to infection causing both pulmonary diseases and diarrhea Sanderson (1957) found that specimens of Oedipomidas oedipus die for no apparent reason

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Šercer & Krmpotić (1959) were of the opinion that a labyrinth, similarly suspended among the pneumatic spaces and connected to the petrous walls only by some fragile osseous lamina may behave like a compass and be able during the evolutionary period to conserve its position in space independent of the positional changes of the surroundings

Werner (1960 (1) (2)) described in Lemurs Cercopithecus Leontocebus (Midas) extensive pneumatic spaces surrounding the semicircular canals and the subarcuate fossa The cochlea becomes conspicuously prominent as a promontory as a consequence of the hollowing out of the bulla in many points He differentiated the bony mantle of the tympanic region from the tympanic bulla giving it the name of capsula ossea tympani In Prosimiae the ventral (jugular) boundary of the spaces of the middle ear is formed by a thin and convex plate blown up to form the osseous bulla

Seiferle & Wustenfeld (1952) explained that in Saimiri the tympanicum remains completely independent without participating contrary to the majority of mammals in the formation of an os tympanicum They gave the number of the turns in the cochlea in Lemuroids as being 2 1/2

Igarashi (1964) gave a detailed study of the inner ear of the squirrel monkey (Saimiri sciureus) with a large number of instructive illustrations He called—with perfect justification—the pneumatization huge *tremendous* anteriorly and even medially from the cochlea The latter *he found almost* entirely surrounded by air spaces including the carotid *artery and the* posterior semicircular canal The carotid artery is located *between the periostal zone of the otic capsule and the round window* is *extremely deep* The latter we found to be more wide than deep and more *exposed to direct view* from the external meatus (less hidden by the promontorial *spur) than in man*

Eggston & Wolff (1947) have shown (Fig 85) highly pneumatic temporal bones *in Macacus rhesus* and mentioned that accumulating data point to the possibility *that the negro petrosa is more highly* pneumatic than the white man's In their Figs 88 and 89 supra infra and retro labyrinthine cells are much *in evidence*

The location of the *carotid artery within the* osseous walls of the cochlear capsule in *our specimens* was very conspicuous (Figs 2 3 6 7 and 11) penetrating *e g into an interscalar septum* Sometimes nothing was left of the capsule except the endothelial lining of the endosteal layer (Figs 2 and 11) Hyrtl (1845 184) discussed by *Kelemen* 1958) speaking of a branch of the *carotid* the stapedial artery was of the opinion that in animals constant *hammering at the thinned out* capsular wall cannot be overlooked The deep penetration of the *carotid* into the cochlear capsule is in these monkeys a very striking phenomenon and must have some *consequences regarding the nature of which no* assumption is justified on the basis of *our present knowledge Kelemen (1963)* discussed and illustrated a very similar condition in human fetuses and newborn A stapedial artery still present in Prosimiae is no longer extant in the Hapalidae

Beattie (1927) described the auditory bulla as a conical structure with its apex lying near the apex of the petrous temporal and with a round base situated more laterally than the apex. In a part of its course the bulla lies close to the great wing of the sphenoid, a circumstance of portent regarding pathology, as will be shown. On the apex is the opening of the auditory tube. The external auditory meatus is wide and the tympanic ring is expanded and fused with the bulla, thereby making it impossible to determine the actual limits of these two parts. There is no mastoid process but the area mastoidea is large. The antero-medial part of the bulla is separated from the postero-lateral compartment by an almost complete bony septum. The antero-medial division consists of a mass of small air cells called the cellulae petrosae. The anterior, funnel shaped end leads into the canal for the tensor and the tube. The cells are continued posteriorly as far as the canal for the internal carotid artery. The latter enters the petrous temporal through a wide foramen situated on the medial wall of the bulla.

Beattie was unable to determine the exact limits of the tympanic and the petrous parts of the temporal bone in the formation of the bulla. The crura of the stapes are fused halfway to their insertion where they suddenly diverge towards the footplate, imitating marsupial conditions. In Hapale there is found the lowest type of ossicle in all the primates. Werner (1960 (1)) illustrated (Fig. 13) this condition in Callithrix jacchus. We generally encountered a stapes of the human type but more elongated, more drawn out in its general contour.

Hang (1933) sketched the extent of pneumatization around the inner ear *in both the tympanic and apical directions. He pointed out* that in Macacus rhesus the septa between the pneumatic spaces are stronger than in Hamadryas. Arrangements in the latter—which, too, becomes a laboratory animal in increasing demand—are practically identical to those found in the squirrel monkey. Meyer (1931) found that the pneumatic system *surrounds the labyrinth, fills the apex and accompanies the eustachian* tube.

Schultz (1952) explained that among all monkeys mastoid processes occur only on Anthropoids.

Hill (1957) characterized the bulla in Platyrrhini as a conical inflation with its apex anteriorly near the apex of the petrosal, the base rounded and lying immediately medial to and below the external auditory meatus. The apex fails to meet the pterygoid lamina. The tympanic ring is enlarged and fused with the opening of the bulla, but there is no bony external meatus. The interior of the bulla is almost completely divided into two chambers by a bony septum, these chambers being antero-medial and *postero-lateral*.

Tumarkin (1957) illustrated these conditions (Fig. 6 E) and pointed out that marmosets have a well developed bulla; in addition they have accessory multicellular systems, both anteriorly in the petrous and posteriorly in the mastoid.



Fig. 2 Callicebus cupreus Gomori impregnation. ×7 Undivided mastoid, tympanic, and apical space surrounding the internal ear, which projects freely into the tympanic part of the common cavity

fection already established or whether the latter developed in captivity Ear infection follows respiratory conditions and, as the latter attract more attention it is possible that knowledge regarding ear pathology will increase in this roundabout way

As in small laboratory animals, easier drainage through the shorter eustachian tube may be a factor of importance Evacuation is further facilitated by the funnel-shaped opening of the apical cells into the tympanic tubal orifice We observed one instance where the tube opened into a single cell which formed a wide bay This easy drainage has the consequence that tympanic perforation does not so readily follow even a suppurative inflammation as in humans Consequently, simple inspection of the external canal for pus is not a reliable method of determining the presence of an otitis media Larger central tympanic membrane perforations show the inward folding of the skin layer, to cover the edge of the perforation, as it does in humans Previous to perforation an abscess may develop between the layers of the drum and postpone the moment of definitive opening Fig. 1

The leading feature of the pathology of the *middle ear* is the fact that



Fig 1 Oedipomidas oedipus Heidenhain Mallory × 95 Tympanic membrane with abscess between epidermal and mucosal lining both still intact

Pathological Observations

As our studies were restricted to the cranial base there was no way to list any *co existing disease* that may have been present in other regions such as pulmonary intestinal parasitic and other

A simple tabulation reports the *frequency of infections* in general and where present distribution in a single or in both ears Among the 48 ears of the 24 animals 25 were free and 23 infected

In studies on non experimental pathology of the small laboratory animals it soon became obvious that frequency of infections rises rapidly with advancing *age* In monkeys this point still has to be elucidated In recent acquisitions it is difficult to decide whether the animal arrived with in

TABLE 3

	Free (both ears)	Infected	
		One ear	Both ears
Callicebus (Saimiri)	4		4
Hapale (Marmosets)	6	3	5



Fig. 2. Callicebus cupreus. Gomori impregnation. ×7. Undivided mastoid tympanic and apical space surrounding the internal ear which projects freely into the tympanic part of the common cavity.

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Fig. 1. Oedipomidas oedipus. Heidenhain-Mallory. ×2. Tympanic membrane with abscess between epidermal and mucosal lining, both still intact.

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Fig. 4. Hapale jacchus. Hematoxylin-eosin. ×20. Normal cochlea promontory projecting freely into the tympanic space; round window niche wide, readily accessible from the tympanic cavity without turning around a spur and without necessity to pass a bottleneck.

cranial base was detached by suppurating masses (Figs. 5 and 6) which through this breach created free admission to the endocranium. In human pathology penetration from this point is a very rare phenomenon, hardly reported even at the period when so much attention was given to suppuration of the petrous pyramid. Here, with a real pyramid lacking and the pneumatic system simply extending to the very apex, the danger of propagation becomes similar to that at the tegmen.

The result, an *osteomyelitis of the cranial base* (Fig. 7), carries an almost invariably lethal prognosis, especially in these mostly unrecognized and untreated cases. This very characteristic picture follows from the undivided nature of the peritympanic cell group, and so pathology as well as anatomy pleads for the term 'peritympanic' instead of the anthromorphic *division in mastoid process and petrous pyramid* (Fig. 8).

The bony septa of the pneumatic cells in some instances showed signs of destruction, but this was a rare occurence. Generally, rather than a few osteoclasts, long seams of osteoblasts were lined up. Resorption buds which reached from the submucosa of the pneumatic cells into the mass filling

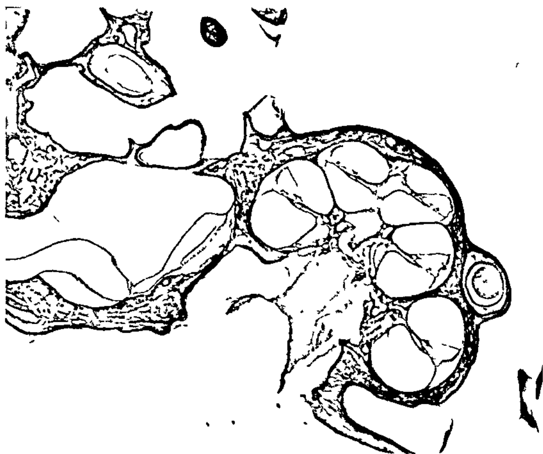


FIG 3 Hapale jacchus Hematoxylin eosin ×24 Normal mid-modiolar cochlea, maci sacculi, stapes, facial

the cavity presents an undivided space, by substitution for a mastoid a a petrous tip, simply of agglomerates of pneumatic cells (Figs. 2, 3 and Together with the central tympanic cavity a single unit is created with part able to escape infection rooted in any of the other parts The resi is an absence of instances where either the mastoid or the apical cell gro is affected separately

Accordingly, the *tegmen* cannot be divided into a tegmen antri, tympa and apicis It is a thin plate rarely containing cells, not to mention t rosary of cells so common in humans This tegmen is easily penetrab (Fig 4), and it is obvious that the suppurative process encounters serious obstacle on its way to the endocranium

Besides this situation at the tegmen, another danger point, attacked the suppurative process, is represented by the surroundings of the apic cell group Beattie, and again Hill, discussed the relations of the spheno alae to the bulla In spite of the long margo sphenoidalis of the tempor and the short contact with the body of this bone, penetrations were see occurring against this center together with the basilar part of the occipit bone, where these two bones are joined in the *spheno-occipital synchon drosis* In some instances the lateral cortical of these elements of th

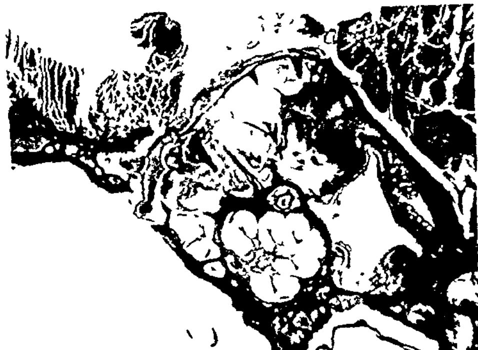


Fig 7 O lipc midas oedipus Heidenhain Mallory ×100 Tympanic membrane (at right) very thick Coel lea carotid penetrating until endosteal layer *is reached* *Spl eno-occipital* ncl ot drosis *penetrated* with complete cortical detachment Coel lear spaces free albeit *surrounded from all sides* by pneumatic spaces filled with pus

Fig 8 Hapale Jacel us Heidenhain Mallory ×15 Eustachian tube (at left Peritubal and hypo tympanic pneumatic cells filled with pus

Fig. 5 Oedipomidas oedipus Heidenhain-Mallory. ×100 Penetration of the dura (above) by suppuration, tegmen (below) corroded by massive secretions.

Fig. 6 Oedipomidas oedipus Heidenhain-Mallory ×100 Cochlea surrounded by pus-filled spaces, remained free. Spheno-occipital junction (at right) invaded Vest[illegible]ule, sub-arcuate fossa free Carotid penetrating the cochlear capsule until [illegible] [illegible]ver is reached



Fig 7 Oedipomidas oedipus Heidenhain–Mallory ×100 Tympanic membrane (at right) very thick Cochlea, carotid penetrating until endosteal layer is reached Spheno occipital synchondrosis penetrated with complete cortical detachment Cochlear spaces free albeit surrounded from all sides by pneumatic spaces filled with pus

Fig 8 Hapale jacchus Heidenhain Mallory ×15 *Eustachian tube (at left) Peritubal* and hypotympanic pneumatic cells filled with pus

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Fig 9 Oedipomidas oedipus newborn Heidenhain Mallory ×25 Serous labyrinthitis Hemorrhage in labyrinthine nucleus perilymph space middle ear

Fig 10 Callicebus cupreus Heidenhain Mallory ×300 Cupula disintegrating Engorged vessel parallel to epithelium of crista

Fig 11 Oedipomidas oedipus Hematoxylin eosin ×75 Massive suppuration in middle ear Serous labyrinthitis in cochlea with organ of Corti intact Carotid penetrating until the endosteal layer is reached Cell infiltrated promontorial mucous membrane



Fig 12 Oedipomidas oedipus Part of Fig 11

Fig 9 Oedipomidas oedipus newborn Heidenhain-Mallory ×25 Serous labyrinthitis. Hemorrhage *in* labyrinthine *nucleus*, perilymph *space*, *middle ear*

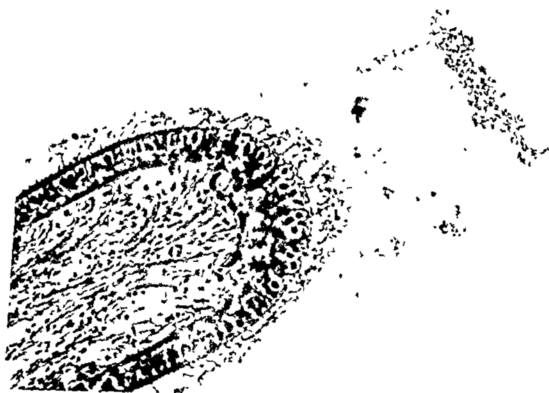


Fig. 10 Callicebus cupreus Heidenhain Mallory ×*300* *Cupula* disintegrating Engorged vessel parallel to epithelium of crista

The intensity of the inflammatory process showed the "toning down", well known from human pathology, in the paralleling of a suppurative process in the middle ear by a sero-fibrinous one in the inner ear. A familiar sight, as *in human pathology*, was pus *outside*, with *sero fibrinous* transudate inside the membrane of the round window. However, involvement of the inner but an intact middle ear was rarely observed.

Among the sensory end organs the *vestibular* ones have shown more resistance again a phenomenon well known from human pathology. Crista with cupula and macula were seen sitting unharmed on a cell filled with pus. The cupula was disintegrating amid secretions (Figs 9 and 10), blood was never encountered in the vestibular endolymph spaces.

Pigment inclusions in the subepithelial layer around the cristae, with preference for the semilunar area, were seen regularly, as already described by Alexander (1901). It occurred in single grains or in clusters of the latter or formed continued strata.

In the *cochlea* the modiolar canal retained its ganglionic elements. Reissner's membrane preserved its original position, deviating from it rarely or at a minimum degree in both directions (Figs 11 *and 12*). The situation within the cochlear duct was remarkably similar to that described in rats (Kelemen, 1963) irradiated with cobalt. The picture offered by the content of the cochlear duct was one of edematous disruption: the elements of the papilla of Corti were scattered as if by *an explosion* showing the tectorial *membrane* thrown against the membrane of Reissner. The latter did not change its position in spite of this "bombardment" by the tectorial, a sign that it withstood, without deformation, the obviously *increased* pressure within the cochlear duct.

Sero-fibrinous secretion was present as in all spaces of the vestibule, in all turns of the cochlea or only in one part of these (Figs 9, 10, 11 and 13). The organ of Corti was either disintegrating amid the *pathological* secretions or intact in spite of the filling of the cochlear duct by transudate.

Igarashi found that initiation of post-mortem changes is effected *in* the area of the inner hair cells and inner supporting cells. This observation was fully affirmed; the mechanism of elective damage to the internal as against the external hair cells was discussed by Kelemen (1956).

In view of experimentation it should be re-emphasized that the cochlea offers good accessibility inasmuch as it projects into the tympanic space, its entire circumference is *free* and has not to be approached through dense masses of otic capsular bone. A labyrinthine nucleus does not stand in the way because in consequence of the "tremendous" (Igarashi) pneumatization it does not exist.

In a newborn marmoset with otitis media presence of lanugo particles amidst the secretions in the middle ear (Fig. 13) gave evidence of intrauterine origin and conforms with the intrauterine foreign body otitis familiar from human pathology.



Fig 13 Oedipomidas oedipus, newborn Hematoxylin eosin ×75 In tympanic cavity debris of lanugo hair with cellular infiltration

the cells, were present but not numerous All in all, the delicate bony partitions resisted the impact of the inflammatory process Fibrinous islands within the content of the cells could be explained as signs of organization New bone formation, conspicuous according to Friedmann (1955) in acute and chronic (experimental) otitis of the guinea pig, according to Tabor (1962) in the dog, and a number of other experimentators in the usual laboratory animals, was not a feature in our monkeys This is parallel with the condition seen in humans in whom extensive deposition of new bone represents a rather rare phenomenon

Meyer found that even after (experimental) short, strictly localized chemical irritation the entire widely ramified pneumatic system can react with inflammatory phenomena, including severe organization adhesions, bone formation, stapedial ankylosis and bony occlusion of the windows

The sharp division of the middle ear from the *inner ear* manifestations is remarkable even in humans, with the otic capsule protected by being built into more solid surroundings, it is more noteworthy here where the inner ear is exposed to attacks from all sides Not a single instance of invasion through the capsule of the inner ear was observed The same was the case around the subarcuate fossa, surrounded by pneumatic cells filled by pus, its walls showed a higher degree of resistance than the surrounding portions of the tegmen

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RÉSUMÉ

Il existe chez le marmouset une large communication entre les cellules pneumatisées de la mastoïde et du pyramide d'une part et la cavité tympanique d'autre part une cavité unique, non divisée est présente. L'absence totale des cloisonnements favorise donc la propagation d'un processus infectieux dans toute la région. La pénétration du tegmen se fait partout avec facilité elle est d'ailleurs également fréquente. On a retrouvé l'invasion du groupe de cellules surtout à la hauteur de la synchondrose spheno occipital. Le point de départ et tient les cellules apicales. Cette invasion est l'équivalent d'une ostéomyélite de la base du crâne.

La fréquence d'otites moyennes avec complication endocrânienne léthale égale les autres causes habituelles de mort telles que maladies pulmonaires, intestinales ou parasitaires. L'oreille interne est entourée de cellules pneumatisées. Malgré sa position dans un milieu aussi exposé elle est moins susceptible aux infections. C'est à un stade séro fibrineux qu'une infection purulente de l'oreille moyenne est atténuée en cas d'extension vers l'oreille interne. Jamais encore on n'a retrouvé une suppuration pénétrant la capsule otique. La disposition anatomique entourant la cochlée et le vestibule a pour conséquence leur accessibilité facile de toutes les directions une circonstance très avantageuse dans un travail expérimental sur l'oreille interne.

ZUSAMMENFASSUNG

Mastoid und Pyramid bilden mit dem Mittelohr, in Marmosets einen gemeinsamen, einheitlichen Raum. Infektiöse Vorgänge ergreifen das gesamte Gebiet einheitlich. Das Tegmen wird *im ganzen Umfange dieses Bereiches häufig und* leicht durchbrochen mit Freilegung des Zuganges zum Endocranium. Durchbruch der apikalen Zellen in der Gegend der spheno occipitalen Synchondrose ist gleichbedeutend mit einer Osteomyelitis der Schädelbasis. Fortschreiten einer Otitis media zur endokraniellen Komplikation ist als Todesursache wahrscheinlich nicht weniger häufig als andere allgemein erwähnte pulmonaler, intestinaler und parasitärer *Herkunft*.

Die Innenohrkapsel ist in ihrer suspendierten Lage von allen Seiten von pneumatischen Zellen umgeben. Innerhalb ihres Gebietes sind Infektionen weniger häufig als in den Zellen der Umgebung. Vorgänge eitrig im Mittelohr erscheinen im Innenohr meistens in einer milderen sero fibrinösen Form. Eitriges Durchdringen der Innenohrkapsel wurde nicht beobachtet. Schnecke und Vorhof sind von Gegenden des tympanalen und peritympanalen Zellsystems her leicht zugänglich ein Umstand von erheblichem Vorteil bei experimenteller Arbeit am Innenohr.

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ON THE SOUND PRESSURE TRANSFORMATION BY THE HEAD AND AUDITORY MEATUS OF THE CAT

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Anesthetized cats were supported by a canvas cradle in a sound proof chamber and were exposed to a progressive sound wave. A flexible probe microphone was implanted in the external auditory meatus and used to measure the sound pressure in the vicinity of the eardrum. A duplicate probe was used to measure the sound pressure at a point near the center of the cat's head in the absence of the animal. From these measurements the magnitude of the ratio of the sound pressure near the eardrum to that in the free field was determined as a function of frequency. When the ear under study was turned toward the sound source, the sound pressure near the eardrum exceeded the free field pressure appreciably, except at very low frequencies. By measuring the sound pressure near the tragus, the resonance of the external auditory meatus itself could be determined. The data obtained in this study can be used to compare results of experiments in which the acoustic stimulus is measured in terms of free field pressures with those in which the stimulus is measured in terms of the sound pressure near the eardrum.

INTRODUCTION

The cat is used extensively as an experimental animal in auditory research. Two classes of experiments are quite common: first, studies in which more or less intact animals are exposed to sound from a distant source; second, experiments in which specially prepared animals are ex-

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Fig 1*a*



Fig 1*b*

Fig 1*a* Ventral view of skull and casts of auditory meati and pinnae The approximate position of the incision for inserting the probe tube is indicated by the arrow

Fig 1*b* Oblique view of skull and cast of auditory meatus and pinna

close proximity to the eardrum The separation between the probe-tube opening and the eardrum was measured by inserting a length of silk thread into the probe tube after placement of the tube in the slit in the meatus The thread was gently advanced until it touched the eardrum, contact was detected by a slight buckling of the thread The silk was then marked at the near end of the probe tube, withdrawn, and its length compared with the known length of the probe tube The probe tube was then advanced by an amount approximately 1–2 mm[1] less than the difference between the lengths of the probe tube and thread and cemented in place with Eastman 910 Adhesive Care was taken to seal the slit in the meatus around the tube The free end of the probe tube was led out through a small, appropriately placed, slit in the skin The initial incision was then sutured so that the natural position and shape of the pinna were essentially restored

The cat was then placed on a canvas cradle suspended from the ceiling of a soundproof room[2] The animal's head was held in an upright position

[1] Post experimental procedures were carried out on each preparation to examine the probe tube position and the condition of the eardrum The distances from probe tube tip to eardrum were in fact found to range between 1.5 mm and 4 mm

[2] This room about 7 ft × 9 ft × 9 ft in size had perforated hardboard backed by sound absorbing material as wall treatment Curtaining off the animal and covering the door with monk's cloth drapes suspended from the ceiling appreciably reduced wall reflections in the room

posed to sound generated by an electroacoustic transducer that is tightly coupled to the auditory mechanism. In the studies of the first class, the level of the acoustic stimulus is normally specified in terms of the sound pressure existing in the sound field in the absence of the animal, i.e. the free-field sound pressure. A microphone calibrated in terms of free-field sound pressure is required to specify the stimulus quantitatively. In the experiments of the second class, the level of the acoustic stimulus is normally specified by measuring the sound pressure at or near the eardrum with a calibrated probe-tube microphone or a microphone calibrated in terms of the sound pressure at its diaphragm.

It is clear that, in a given sound field, the free-field sound pressure and the sound pressure at the eardrum will generally not be the same, except at the very low audible frequencies. At low frequencies, the wavelength of sound is long compared with the dimensions of the animal's head, pinna and ear canal, and the sound pressures in the region of the head are essentially uniform.

As the frequency of the sound increases, the wavelength becomes comparable with, or smaller than, these dimensions. Resonance occurs in the auditory canal and the incident sound wave is reflected from and diffracted by the head and pinna, with the result that the sound pressure near the eardrum is often appreciably different from that in the free field. This pressure transformation, expressed as the ratio of the two pressures, depends on frequency and on the angle of orientation of the animal with respect to the incident sound wave. This pressure ratio is essentially predictable by the geometry of the configuration and by wave-acoustical principles. It has been quantitatively studied in man (v. Békésy, 1932, Langenbeck, 1931, Wiener & Ross, 1946, Wiener, 1947). No comparable data for the cat exist, to the best of our knowledge, and for this reason the present study was undertaken.

TECHNIQUE

Figure 1 consists of two photographs of a cat's skull, with Cerrobend (an alloy of 155°F melting point) casts of the auditory meatus and pinna set in place. It is seen that, beginning at the eardrum, the external meatus consists of an essentially cylindrical portion which extends in a direction approximately normal to the sagittal plane (Fig. 1 *a*), thereafter it bends sharply at an almost right angle, changing its cross section from an approximately circular one to a narrow dumbbell-shaped opening, which leads to the pinna (Fig. 1 *b*).

In the experiments described here, the cartilaginous external auditory meatus was exposed by a ventral surgical approach. A small, flexible, plastic probe tube (1.3 mm inside diam., 2.0 mm outside diam., 27 mm length) was inserted into a small lengthwise slit in the posterior-ventral side of the straight portion of the meatus (Fig. 1 *a*) so that it was in

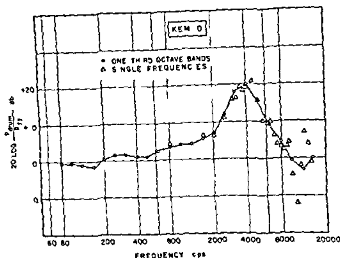


Fig. 3. A comparison between the ratio of the sound pressure *in decibels* at the eardrum to the free field pressure obtained for one third octave bands of random noise and single frequencies.

the data are presented in terms of pressure ratios. Nevertheless, a direct calibration of the probe tube carried out in the free field by means of a Bruel and Kjaer 1/2 inch condenser microphone showed a response curve free from sharp peaks and dips.

By means of the implanted probe tube the sound pressures at the ear drum were measured as a function of frequency. The sound pressures in the free field—in the absence of the cat at a location corresponding to the midpoint between the animal's ears—were made by means of a duplicate piece of plastic probe tube. This duplicate probe was also used to measure the sound pressure near the tragus.

Seven cats were used for these experiments. Data from two cats were discarded because post-experimental examination disclosed damaged ear drums which were probably due to accidental inward movement of the probe tube implant during experimentation. In one instance measurements of the pressure near the eardrum in a surgically shortened meatus were made *before and after the drum was deliberately damaged.* The sound pressures measured in the vicinity of the punctured drum at 1 kcps and 3.5 kcps were 10–15 dB below those measured at these frequencies near the intact drum. In the remainder of the frequency range the data differed by less than 3 dB.

The use of one third octave bands of noise made it possible to average over the irregularities in the loudspeaker response and those caused by room reflections. By the same token it was not possible to examine the fine structure of the pressure transformation function. Figure 3 shows a comparison between a typical pressure transformation function obtained using one third octave bands of noise and data points obtained for the

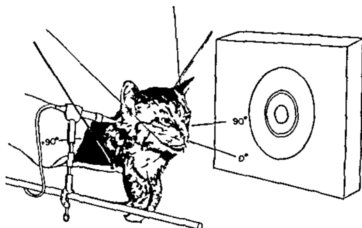


FIG 2 Sketch of the animal suspended in the cradle The loudspeaker is in position for measurements at −90° azimuth

by a silk thread passing through the cat's mouth (Fig 2) The probe microphone (Bruel and Kjaer 4134, $^1/_2$ inch, with Kit UA 0040) and pre-amplifier (Bruel and Kjaer 2615) were supported on a fixed rod with laboratory clamps A short piece of metal probe tube of 1 mm outside diameter was inserted 12 mm into the implanted plastic tube (the outside diameter of the metal probe tube had been built up for a snug fit into the plastic tube) and the assembly secured The convention used to designate the orientation of the axis of the loudspeaker relative to the center of the cat's head is indicated in Fig 2 Thus, an azimuth of +90° denotes the loudspeaker oriented directly toward the tested ear, regardless of whether it was on the right or the left

Random noise, passed through a one-third octave band filter set (Bruel and Kjaer 1612) and a General Radio 1390-P2 pink-noise filter, was amplified and delivered to the animal via an Altec-Lansing 755-C loudspeaker *enclosed in a wooden box, approximately 12 in × 15 in × 5 in* in size The free-field signal levels for all experiments[1] were 100 ± 5 dB re 0 0002 μbar for one-third octave band center frequencies from 100 cps to 10 kcps The average sound-pressure levels at center frequencies of 50 cps, 12 5 kcps and 15 5 kcps were about 88 91 and 85 dB re 0 0002 μbar, respectively Signal-to-noise ratios far exceeded 10 dB in most cases Readings with signal-to-noise ratios of less than 10 dB, which were encountered occasionally, were discarded Measurements conducted in the free field with the probe tube opening closed with a tapered metal plug indicated that the contribution from sound passing through the wall of the probe tube and microphone fixture was insignificant Thus, the microphone output was essentially determined by the sound pressure existing at the open end of the plastic probe Probe tube corrections were not needed, since

[1] Because of space limitations a spherical progressive sound wave rather than a plane progressive sound wave was generated, the loudspeaker to animal distance was approximately 17 inches

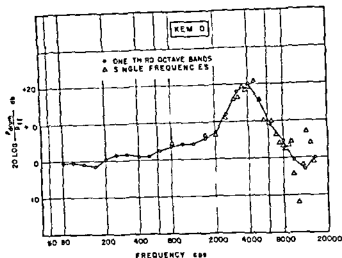


FIG 3 A comparison between the ratio of the sound pressure in decibels at the eardrum to the free field pressure obtained for one third octave bands of random noise and single frequencies

the data are presented in terms of pressure ratios Nevertheless a direct calibration of the probe tube carried out in the free field by means of a Bruel and Kjaer 1/ inch condenser microphone showed a response curve free from sharp peaks and dips

By means of the implanted probe tube the sound pressures at the ear drum were measured as a function of frequency The sound pressures in the free field in the absence of the cat at a location corresponding to the midpoint between the animal s ears were made by means of a duplicate piece of plastic probe tube This duplicate probe was also used to measure the sound pressure near the tragus

Seven cats were used for these experiments Data from two cats were discarded because post-experimental examination disclosed damaged ear drums which were probably due to accidental inward movement of the probe tube implant during experimentation In one instance measurements of the pressure near the eardrum in a surgically shortened meatus were made before and after the drum was deliberately damaged The sound pressures measured in the vicinity of the punctured drum at 1 kcps and 1.5 kcps were 10 15 dB below those measured at these frequencies near the intact drum In the remainder of the frequency range the data differed by less than 5 dB

The use of one third octave bands of noise made it possible to average over the irregularities in the loudspeaker response and those caused by room reflections By the same token it was not possible to examine the fine structure of the pressure transformation function Figure 3 shows a comparison between a typical pressure transformation function obtained using one-third octave bands of noise and data points obtained for the

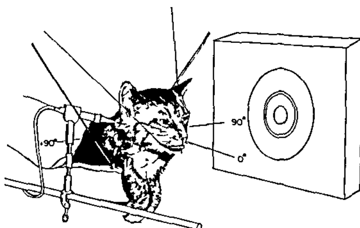


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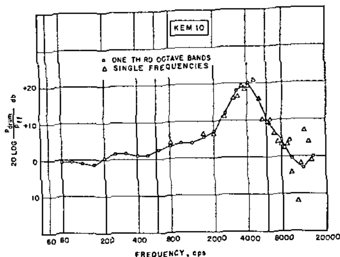


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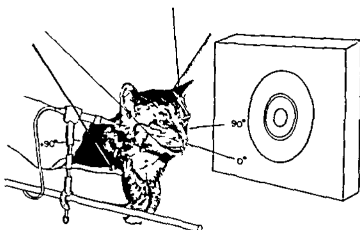


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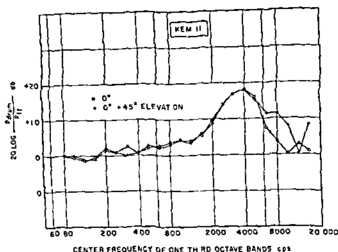


Fig. 5. The effect of source elevation (+45°) on the pressure transformation between free field and eardrum for one cat (KEM 11) for 0° azimuth.

the pressure ratios for negative azimuths were found to be somewhat below 0 dB is probably a consequence of the use of a spherical rather than of a plane sound field. In a low-frequency plane progressive sound wave, a pressure ratio of very nearly zero decibels obtains at all azimuths.

These pressure ratios were obtained from measurements taken with the axis of the loudspeaker approximately horizontal and pointing at the center of the cat's head. Figure 5 shows the effect of a 45° elevation of the loudspeaker at 0° azimuth. The distance between loudspeaker and animal was kept constant. Only small differences between the pressure ratios are

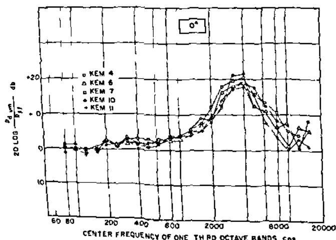


Fig. 6. The ratio in decibels of the sound pressure at the eardrum to the free field pressure as a function of frequency for five cats for 0° azimuth.

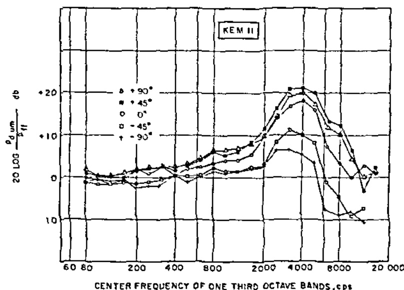


Fig. 4 The ratio of the sound pressure, in decibels, at the eardrum to the free field pressure as a function of frequency for one cat (KEM 11) and five azimuths

same preparation using single frequencies It is seen that below about 10 kcps these two functions are in close agreement The averaging effect of the filters is quite evident for frequencies above 10 kcps

There are several limitations and omissions in this study the orientation of the animal was limited to azimuths such that the sound wave approached from the front or side, except in a few exploratory experiments, animal and sound source were in the same (horizontal) plane, and no attempt was made to investigate a large population of cats The pressure distribution across the eardrum at high frequencies, the effects of possible activation of the middle ear muscles during presentation of the stimulus and the effects of anesthesia were not investigated It is our opinion that these factors are not likely to affect the results in a major way

RESULTS

A *Pressure Transformation between Free Field and Eardrum*

Figure 4 shows, for one cat, the ratio of the sound pressure at the eardrum to the free-field pressure as a function of frequency for five azimuths As expected, for positive azimuths the sound pressure at the drum is appreciably greater than that in the free field, except at very low frequencies The maximum pressure ratio was obtained for an azimuth of +45°—about 21 dB at approximately 4 kcps At this azimuth the plane of the pinna entrance is roughly perpendicular to the loudspeaker axis At negative azimuths, when the ear under test is turned away from the source, the pressure ratios are smaller This can be attributed to sound diffraction and shielding by the head and pinna and is especially noticeable at the higher frequencies The fact that even at the very low frequencies

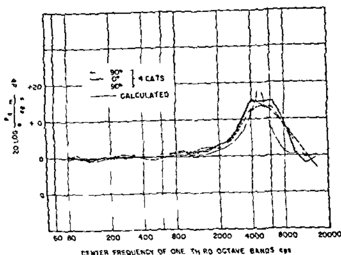


FIG 8 The mean ratio in decibels of the sound pressure at the eardrum to the sound pressure at the entrance of the external meatus (tragus) for four cats as a function of frequency with azimuth as the parameter

the pressure ratios for man at medium and low frequencies tend to be somewhat greater than those of the cat Otherwise the pressure transformation functions are remarkably similar In man as in the cat the highest pressure ratios are found near an azimuth of +45 degrees It should be noted that in man above about 1 kcps the pressure ratios for 0° azimuth are generally smaller than the corresponding ratios for +90° whereas in the cat they are about the same The fact that the pressure ratio in the cat does not vary greatly from +90° to 0° azimuth may be attributed to the much larger size of the pinna relative to that of the head It appears that for some azimuths despite the smaller size of its head the pressure ratios in the cat can change as strongly with azimuth as they do in man

B *Pressure Transformation between Entrance of the Auditory Meatus and Eardrum*

Since a convenient reference plane for defining the entrance to the auditory meatus is lacking in the cat we have decided in this study to use a reference position defined by the tragus Determinations of the ratio of the sound pressure at the eardrum to that at the entrance to the auditory canal were carried out for most of the cats for which the pressure transformation between free field and eardrum were reported above Data were obtained on four cats for +90° 0° and 90° azimuths Perhaps because of the uncertainty in the positioning of probe near the tragus the variability of the high frequency pressure ratios among animals turned out to be somewhat greater than that found for the eardrum to free field

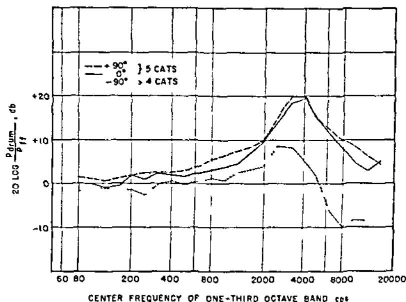


Fig 7 The mean ratio, in decibels, of the sound pressure at the eardrum to the free field pressure for several cats as a function of frequency, with azimuth as the parameter

apparent for frequencies up to about 5 kcps, above that frequency, a somewhat higher pressure ratio is obtained with the elevated sound source

Figure 6 shows the pressure transformation functions for 0° azimuth obtained with five cats It is seen that the pressure ratio rises gradually from near zero decibels at 80 and 100 cps to a broad maximum of about 20 dB in the vicinity of 4 kcps This peak is due to the pressure increase caused by sound diffraction by the head and pinna and by resonance in the auditory canal As the frequency increases above 4 kcps, the pressure ratio falls rapidly to 5 dB or less in the vicinity of 10–12 kcps Similar graphs for the +90° and −90° azimuths, not presented here, show a different frequency dependence but similar variability from animal to animal

Figure 7 shows the mean values of the pressure ratios for +90°, 0° and −90° azimuths derived from these data Since the spread of the data was relatively small, the arithmetic mean of the pressure ratios in dB was calculated and plotted as an approximation for the mean sound pressure ratios It is interesting to note the similarity of the functions for 0° and +90° azimuths It can be inferred from Fig 4 that the pressure transformation function for +45° azimuth would lie close to, but probably slightly above, the data obtained for +90° The function for −90° azimuth shows a maximum of greatly reduced level occurring at approximately 3 kcps As the frequency increases, the magnitude of the pressure ratio decreases still more In fact, at 8 kcps a pressure gain of +10 dB measured for the +90° azimuth becomes a pressure loss of −10 dB for the −90° azimuth

It is interesting to compare these data with the corresponding functions for man (Wiener, 1947) Because of the larger size of the human head,

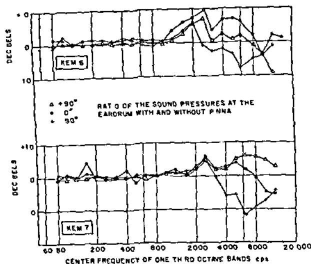


Fig 9 The ratio of the sound pressures measured at the eardrum with pinna intact and with the external parts of pinna surgically removed (two cats)

C *Acoustical Effect of the Presence of the Pinna*

It is of some interest to examine the effect of the external parts of the pinna on the pressure transformation between free field and eardrum in the cat After determination of the pressure ratio with pinna intact, the external parts of the pinna were removed surgically and the pressure ratio was again determined The results obtained for two cats are shown in Fig 9 It is seen that the presence of the pinna results in some increase in the pressure above about 1 kcps for angles of +90° and 0° For an angle of −90° the opposite is true, above about 3 kcps the presence of the pinna shields the auditory canal which results in a reduction of the magnitude of the pressure transformation These results while generally indicative of the acoustical effect of the pinna are only preliminary because different amounts of pinna were removed in the two animals tested Accurate control of pinna removal was difficult

APPLICATIONS

As one illustrative example of the utility of the pressure transformation functions presented in this study consider the recent work on the effects of noise on the cat by Miller, Watson & Covell (1963) in which the auditory threshold of the cat was studied In these threshold determinations an avoidance response was elicited from the animal under test which consisted of crossing a hurdle in the center of the cage The level of the corresponding sound pressure was inferred from free field sound pressure measurements in an approximately uniform progressive sound field The authors state that the left cochleas of all experimental animals used in their

pressure ratios. Nonetheless, the mean values of the pressure transformation function from the vicinity of the tragus to the eardrum were found to be essentially independent of azimuth, as expected (see Fig. 8).

This figure shows that the ratio of the pressure at the eardrum to that at the tragus is essentially zero decibels for frequencies below about 1 kcps, it then rises to a broad maximum of about 14 dB between 4 and 6 kcps, and falls again toward 0 dB near 12 kcps. Sp. Kirikae (1960) calculates the "resonance frequency" of the external auditory meatus of the cat to be 4100 cps. At its maximum, the mean pressure ratio in the auditory meatus is seen to be about 5 dB less than the maximum mean pressure ratio between eardrum and free field. A detailed comparison with the data for man (Wiener & Ross, 1946) is not easily made because of the difficulties in specifying a reference entrance plane for the purposes of sound-pressure measurement in the cat's meatus.

In an attempt to account for the experimental data, a model of the external auditory meatus consisting of two sections of a rigid tube of small but different cross sections was used. A rigid termination perpendicular to the axis is assumed. The first section, determined from anatomical measurements to be $l_1 = 1.5$ cm long, is designed to simulate the cylindrical part of the meatus from the eardrum to the bend in the canal, the second tube, assumed to be twice as large in cross-section area and $l_2 = 0.5$ cm long, is designed to simulate the portion of the auditory canal from the bend to a plane through the tragus perpendicular to the axis of this latter portion. Finally, it was assumed that the pressure was measured at 0.4 cm from the rigid termination (eardrum). $x = 0$ denotes the entrance to the artificial meatus. Assuming plane waves and no dissipation, the ratio of the sound pressure at a position x to that at the entrance is given by

$$\frac{p_x}{p_o} = \frac{\cos k(l_1 + l_2 - x)}{\cos kl_1 \cos kl_2 - S_2/S_1 \sin kl_1 \sin kl_2}$$

S_1 and S_2 are the respective cross-section areas of the tubes of length l_1 and l_2, and $k = 2\pi f/c$, where f is the frequency, and c the speed of sound.[1] Using the numerical values given above, the mean squared pressure ratio in each one-third octave band was evaluated according to the equation above by means of a digital computer. The results are shown in Fig. 8. The calculated pressure ratio is seen to be in reasonably good agreement with the observed data below the resonance frequency; above that frequency it is not. This is not surprising as the effects of differences in length, shape, absorption, etc. between the model and an actual auditory canal are expected to be more pronounced at the high frequencies than at the low ones.

[1] Note that for $S_1 = S_2$ and $x = l_1 + l_2$ the pressure ratio becomes $(\cos k(l_1 + l_2))^{-1}$ corresponding to that in a tube of uniform cross section and length $l_1 + l_2$.

behavioral threshold function between about 2 kcps and 7 kcps appears to be reasonably well reproduced in the neurophysiological data. This notch is probably related to the fact that in the cat the middle ear cavity is divided by a bony septum into two volumes which are connected by a small hole (Møller, 1965).

DISCUSSION AND CONCLUSIONS

From the available data and within the limitations of this study, the following conclusions can be drawn.

1. In an approximately spherical sound wave, the transformation between the free-field pressure measured near the center of a cat's head and the sound pressure near the eardrum is essentially unity below about 300 cps, independent of the source orientation. Above about 1.5 kcps the pressure ratio increases markedly in magnitude and becomes more dependent on the orientation of the animal's head with respect to the incident sound wave. When the pinna is oriented directly toward the source, the pressure ratio reaches a maximum of about 20 dB around 4 kcps. At that frequency, the pressure ratio at the ear pointing away from the source is about 15 dB lower. This directionality increases to about 20 dB at 8 kcps, where the magnitude of the pressure ratio for an azimuth of +90 degrees has dropped to 10 dB, and to −10 dB for −90°. This high directionality is achieved in the cat in large measure by the comparatively large size and appropriate shape of the pinna. Despite the much larger head size, man exhibits no greater directionality at high frequencies than does the cat.

2. In contrast to man, the auditory canal of the cat contains a sharp 90° bend. The cross section of the meatus changes from nearly circular in the vicinity of the eardrum to a narrow dumbbell-shaped section near the tragus. It may be that this accounts, in part, for the broader peak in the resonance curve of the auditory canal, as compared with man.

3. It is not expected that the shape and magnitude of the pressure transformation functions would have changed appreciably had the separation between sound source and animal been increased to produce an essentially plane progressive wave. It was not possible to do this because of space and other limitations.

4. The pressure transformation between entrance and termination of the auditory canal calculated from a model accounts for the measured mean resonance frequency. Also, the calculated magnitude of the pressure ratio agrees with the measured data below the resonance frequency, but not above.

5. The pinna of the cat is supported by cartilaginous tissue with many involutions and convolutions. In its approximately normal position, the presence of the pinna increases the sound pressure at the eardrum in the frequency range above 1 kcps when the ear is on the same side of the

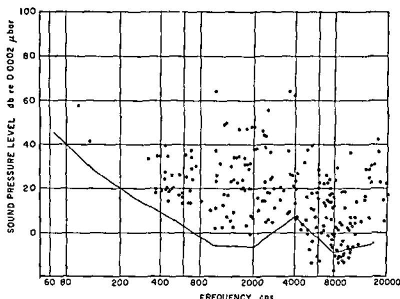


Fig. 10. The minimum audible pressure function for cats derived from threshold data (after Miller *et al.*) compared with the threshold responses of single auditory nerve fibers (after Kiang *et al.*) as given by the open circles.

study were surgically destroyed before conducting the experiments, and it appears that the orientation of the animal's head with respect to the sound source before responding was not controlled or known. Therefore, we decided to consider here the above mentioned authors' "best estimate" of the minimum audible field from their own and several other studies. In order to transform the minimum audible field into minimum audible pressure, we use the pressure transformation function for 0 degrees of the present study (Fig. 7), and make the following assumptions: the animal is in a reasonably uniform sound field, it orients its head toward the sound source, the sound source and animal are in an approximately horizontal plane and the present data are approximately applicable for single frequencies. Figure 10 shows the minimum audible pressure function thus obtained.

Kiang, Watanabe, Thomas & Clark (1965) have obtained threshold responses of single auditory nerve fibers of cats whose auditory mechanism was energized by a condenser transducer closely coupled to the eardrum with the pinna and a portion of external meatus removed. The pressure near the eardrum was monitored by a probe microphone. The results of these measurements, corrected for source and probe tube response, are also shown in Fig. 10 (open circles). It is seen that the great majority of the circles lies above the minimum audible pressure function derived from the threshold data of Miller *et al.* as discussed above.[1] The "notch" of the

[1] If the 'closed ear effect' (Wever & Lawrence 1954) were operative the low frequency portion of this function could be shifted upward to account for this phenomenon.

des Schalldruckes in der Nahe des Kopfes der Katze nach Entfernung des Tieres verwendet Aus diesen Messungen konnte man die Grosse des Verhaltnisses des Schalldruckes am Trommelfell zu dem im Freifeld gemessenen Schalldruck als Funktion der Frequenz bestimmen War das untersuchte Ohr zur Schallquelle gerichtet so ist der am Trommelfell gemessene Schalldruck wesentlich grosser als im Freifeld mit Ausnahme der sehr niedrigen Frequenzen Durch Messungen des Schalldruckes in der Nahe des Tragus konnte die Resonanz des Gehorganges selbst bestimmt werden Die Resultate dieser Arbeit konnen zum Vergleich der Ergebnisse von Experimenten benutzt werden in welchen der akustische Reiz als Freifeld Schalldruck bzw als Schalldruck am Trommelfell gemessen wurde

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sound source. When the ear in question is turned away from the sound source, the opposite is true The fact that the animal is capable of rotating the pinna and orienting it at will leads one to infer that by doing so the cat can increase the pressure transformation for a given source and thereby hear better, or discriminate better against other sources[1]

6 Because the pressure transformation caused by the head, pinna and auditory meatus appreciably modifies the sound pressure acting on the eardrum as compared with the sound pressure in the free field, this fact must be taken into account when comparing the results of different auditory studies on the cat

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RESUME

Des chats anesthésiés maintenus au moyen d'un harnais de tissu dans une chambre sourde ont été exposés à une onde sonore progressive Un microphone au bout d'un sonde flexible a été introduit dans le méat auditif externe pour mesurer la pression sonore à proximité du tympan On a employé une sonde analogue pour mesurer la pression sonore à un point en champ libre correspondant au centre de la tête du chat en l'absence d'animal A partir de ces mesures le *rapport de la pression sonore près du tympan à la pression en champ libre* a été déterminé en fonction de la fréquence Lorsque l'oreille étudiée est tournée vers la source sonore, la pression sonore près du tympan dépasse de façon appréciable la pression en champ libre, sauf pour les fréquences très basses Les mesures de la pression près du tragus ont donné l'effet de résonance du méat auditif externe seulement Les résultats obtenus dans cette étude peuvent être employés pour comparer les résultats d'expériences dans lesquelles le stimulus acoustique est mesuré en termes de la pression en champ libre aux résultats d'expériences dans lesquelles le stimulus est mesuré au moyen de la pression sonore près du tympan

ZUSAMMENFASSUNG

In einem schallisolierten Raum wurden Katzen unter Narkose unterstützt durch eine Segeltuchwiege, einer fortschreitenden Schallwelle ausgesetzt Eine biegsame Mikrophonsonde wurde in den Gehörgang des Tieres eingesetzt, um den Schalldruck am Trommelfell messen zu können Eine gleiche Sonde wurde zur Messung

[1] Note the functional similarity between this and man made devices such as the microwave receiving horn which can be rotated about a horizontal axis to receive the signal from communication satellites optimally in signal level and freedom from interference (Hines, Li & Turrin 1963)

Everberg (1960 *d*) regarded some of the above-mentioned diseases as the "probable" cause of unilateral deafneses in 17 cases and as its "definite" cause in 3. Lehnhardt's (1962) series of 45 cases showed the following etiology:

mumps	68 per cent	labyrinthitis	4 per cent
congenital	24	asphyxia	2

Deafness was attributed to mumps if the complement fixation test for mumps was positive in the dilution of 1:20.

Unilateral deafness is usually detected accidentally and sometimes fairly late. Less than half (47.5 per cent) of the 122 cases reported by Everberg (1960 c) had been detected before the children entered school or during the first school year. This means that about half of the congenital cases and of those acquired in early childhood had escaped notice at the first hearing test at school.

Everberg (1960 *a, b, c*) studied his series thoroughly and found in caloric tests that vestibular function was absent on the deaf side in 34 cases (28 per cent) and preserved in 88 (78 per cent), this number including one case with impaired and 87 with normal function. Lehnardt (1962) obtained no vestibular response when mumps had caused the lesion. Pascher (1963) reported normal vestibular response in 13 cases out of 26, diminished function in 4, and no response in 3.

Everberg's (1960 *b*) x-ray studies of the inner ear showed abnormalities in the deaf ear in 22 cases out of 122. The tomograms in 20 cases revealed two types of abnormalities. In type I (18 cases) the inner ear cavity was not discernible and in type II (2 cases) the vestibule and lateral semicircular canal formed one large cavity. Type I represented osseous obliteration of the inner cavities—a probable result of labyrinthitis. Congenital obliteration was reported in 5 cases. Lehnhardt (1962) emphasized the difficulties in assessment of the tomograms. He found malformation of the inner ear in two cases out of 45 but no obliteration of the inner cavities.

MATERIAL AND METHODS

Children in Finland enter primary school at the age of 7. In Helsinki their hearing is tested one year before school entrance, and thereafter in the first, third, sixth and eighth school year. Hearing tests by pure tone audiometry are made by trained nurses. Pupils with impaired hearing are examined by the school otologist.

During the period 1963–65, 28 cases of unilateral deafness with normal hearing in the other ear were found among 30 882 pupils, an incidence of 0.09 per cent. Twenty-seven pupils, 15 boys and 12 girls attended for examination. The youngest pupil was 7 years and the oldest 16 years old. Average age was 10 years.

UNILATERAL DEAFNESS IN CHILDREN

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From the Helsinki University Otolaryngological Hospital (Head: Prof. Urjo Siirala) and the Elementary School Health Service (Head: Sakari Lahdensuu), Helsinki

During the period 1963–65, 28 cases of unilateral deafness with normal hearing in the other ear were found in Helsinki among 30 882 pupils. *Twenty seven children attended for examination.* Etiology was unknown in 18 cases, mumps in 3, meningitis in 2, cerebral concussion in 2, measles in 1, and maternal rubella in 1. Electronystagmographic studies showed normal symmetrical reaction in 12 cases, canal paresis in both ears in 7, canal paresis in deaf ear in 4, and no response from deaf ear in 4. Radiologic examination showed normal mastoid cells in all cases. Abnormalities of the internal auditory canal were encountered in 6 cases. Etiology of deafness in these six cases remained unknown.

Unilateral deafness with normal hearing in the other ear is a fairly uncommon disorder. Everberg (1960 *c*) estimated the incidence at 0.1 per cent in 183 000 school children. Only a few papers on unilateral deafness and its etiology have been published. Marschak (1931) reported 50 cases and interpreted the etiology as follows:

tympanogenic	27 cases	mumps	4 cases
measles	7	meningitis	3
congenital	7	influenza	2

Kinney (1953) reviewed 310 cases; the etiology was as follows:

unknown	42 per cent	measles	23 per cent
meningitis	24	mumps	11

In Everberg's (1960 *d*) series of 122 children and adolescents unilateral deafness was apparently congenital in 83 per cent and acquired in 17 per cent. In the former group no definite cause was demonstrable in about 50 per cent, hereditary factors had caused deafness in 25–30 per cent and in 9 per cent x-ray appearances revealed that the lesion was due to developmental anomalies in the inner ear. In 21 instances (17 per cent) in which the disease appeared to be acquired, the etiology was:

meningitis	11 cases	scarlet fever	1 case
mumps	5	head injury	1
labyrinthitis	2	sudden idiopathic deafness	1

TABLE 2 *Age at detection of unilateral deafness 27 cases*

Age years	No of cases
4 5	9
6	5
7	9
8	1
9	2
11	1
Total	27

hearing in that ear at the age of 6 This is the single cause of the so-called sudden deafness in this series Deafness appeared in connection with mumps at the age of 6 years in two cases and at the age of 9 in one The recorded age of onset in the case of other diseases was meningitis 1 1/2 years and 4 years cerebral concussion 6 and 9 years and measles 8 years In most cases the etiology appears reliable in view of the relatively late onset of deafness *Age of detection* of deafness is given in *Table 2*

Average age at detection of deafness was 6 years As shown in Table 2, deafness was detected in half of the children before they entered school and in one third while in the first grade When detected later, viz at the age of 8 or more deafness was due in three cases to measles mumps or cerebral concussion Only one child whose deafness was noticed at the age of 9 seemed to have escaped detection in the earlier hearing tests

Hearing tests confirmed the findings of the school otologist In every case the average hearing threshold for the three pure tones (500, 1000 and 2000 cps) was in one ear 20 dB or better, and in the other 95 dB or worse None of those examined was able to hear shouted words when the ear with normal hearing was masked by Barany's noise box

The vestibular apparatus was tested by means of an electronystagmograph Table 3 shows the results Only one child had horizontal spontaneous nystagmus towards the normal ear

TABLE 3 *Electronystagmographic studies in unilateral deafness 27 cases*

Finding	No of cases
Normal symmetrical reaction	12
Canal paresis in both ears	7
Canal paresis in deaf ear	4
No response from deaf ear	4
Total	27

TABLE 1. *Etiology of unilateral deafness according to case histories 27 cases*

Etiology	No of cases
Unknown	18
Mumps	3
Meningitis	2
Cerebral concussion	2
Measles	1
Maternal rubella	1
Total	27

The history was recorded using the questionnaire of Everberg (1960 c) which takes into account every possible cause of deafness After routine ENT and neurological examination, hearing was tested by pure-tone and speech audiometry The intensity calibration of pure-tone audiometers was in accordance with the British Standard (NPL) Because of the approximately 10 dB numerical difference in practical hearing threshold levels for speech (500–2000 cps) between the American and the British Standards for audiometric zero, we have confined the term deafness to speech hearing levels of 95 dB or more Total impairment or deafness is at the level of 83 dB or worse according to the American Standard (Davis & Fowler Jr 1960) As a supplementary test the other ear was masked by Barany's noise box and the patient was asked to repeat words shouted in the other ear

The vestibular apparatus was tested electronystagmographically The children were first tested for spontaneous and postural nystagmus, and after that water at 30°C and occasionally at 44°C was introduced into the ear for 30 secs Radiologic examination of the temporal bone consisted of stereoscopic films in the Runström II, Stenvers and transorbital positions Antibody determinations for mumps in 10 cases were made at the State Serum Institute

RESULTS

Unilateral deafness was right-sided in 15 cases and left-sided in 12 General ear, nose and throat examination was negative in all cases Neurological findings were also on the whole slight two children showed turning about 100 degrees toward the deaf ear in Unterberger's walking test

The *etiology* of unilateral deafness is given in Table 1 on the basis of case histories

As seen above, in two thirds of this series no obvious cause for deafness was found The first group with unknown etiology includes a girl who developed recurring right-sided acute otitis media at the age of 2 years Suddenly without any previous symptoms in the right ear she lost her



Fig 2 Case 17 Right sided unilateral deafness of unknown etiology The internal auditory canal is narrow on the right side (0) Transorbital projection Electronystagmography showed canal paresis on the right side and a normal response on the left

found in all three cases in which deafness was caused by mumps and in one case apparently caused by maternal rubella Bilateral canal paresis was attributed in three cases to measles meningitis or cerebral concussion

X ray studies revealed normal pneumatization in all 27 cases Abnormal findings and the etiology of deafness are given in Table 4 Figures 1 2 show in the transorbital projection the internal auditory canals in two cases

Surprisingly normal mastoid pneumatization was found in case 13 despite recurring acute otitis media on the right side It is difficult therefore to

TABLE 3 *Complement fixation test for mumps in unilateral deafness 10 cases*

Titre	No of cases
< 1/4	1
+ 1/4	1
+ 1/8	7
+ 1/64	1
Total	10

TABLE 4 *Radiologic examination of temporal bone in unilateral deafness Abnormal findings in 27 cases examined, and cause of deafness*

Finding	No of cases	Cause of deafness
Internal auditory canal narrower on diseased side and some *sclerosis around the canal*	4	3 unknown *1* sudden deafness
Internal auditory canal narrower and malformation of ossicles on diseased side	1	Unknown
Internal auditory canal wider on diseased side	1	Unknown
Total	6	

The patient who showed spontaneous nystagmus had no function in the vestibular apparatus in the caloric test The cause of deafness was cerebral concussion In two cases with no response from the diseased ear, the *cause of deafness was unknown The fourth child with no response* had had meningitis at the age of 1 1/2 years Normal vestibular response was



Fig 1 Case 13 Recurring acute otitis media on right side since the age of 2 years Sudden deafness without any other symptoms on the right side at the age of 6 In the transorbital projection the left internal auditory canal is of normal width The canal on the right side (0) *poorly visible and surrounded by sclerosis* Electronystagmography showed canal paresis on right side and normal response on left



Fig. 2. Case 17. Right sided unilateral deafness of unknown etiology. The internal auditory canal is narrow on the right side (0). Transorbital projection. Electronystagmography showed canal paresis on the right side and a normal response on the left.

found in all three cases in which deafness was caused by mumps, and in one case apparently caused by maternal rubella. Bilateral canal paresis was attributed in three cases to measles, meningitis or cerebral concussion.

X-ray studies revealed normal pneumatization in all 27 cases. Abnormal findings and the etiology of deafness are given in Table 4. Figures 1–2 show, in the transorbital projection, the internal auditory canals in two cases.

Surprisingly, normal mastoid pneumatization was found in case 13 despite recurring acute otitis media on the right side. It is difficult therefore to

Table 5. Complement fixation test for mumps in unilateral deafness. 10 cases

Titre	No. of cases
< 1/4	1
+ 1/4	1
+ 1/8	7
+ 1/64	1
Total	10

TABLE 4. *Radiologic examination of temporal bone in unilateral deafness. Abnormal findings in 27 cases examined, and cause of deafness*

Finding	No. of cases	Cause of deafness
Internal auditory canal narrower on diseased side and some sclerosis around the canal	4	3 unknown 1 sudden deafness
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Internal auditory canal wider on diseased side	1	Unknown
Total	6	

The patient who showed spontaneous nystagmus had no function in the vestibular apparatus in the caloric test. The cause of deafness was cerebral concussion. In two cases with no response from the diseased ear, the cause of deafness was unknown. The fourth child with no response had had meningitis at the age of 1 1/2 years. Normal vestibular response was

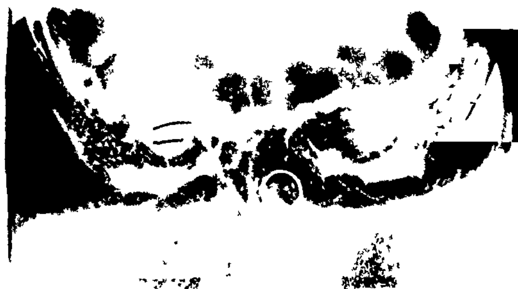


FIG. 1. Case 13. Recurring acute otitis media on right side since the age of 2 years. Sudden deafness without any other symptoms on the right side at the age of 6. In the transorbital projection the left internal auditory canal is of normal width. The canal on the right side (0) poorly visible and surrounded by sclerosis. Electronystagmographs showed canal paresis on right side and normal response on left.

Only in the present study was registration of nystagmus carried out. Vestibular response was normal after maternal rubella and mumps but abnormal in other acquired cases. Though the group is small it may be concluded that vestibular function cannot be taken as a criterion of the hereditary or acquired nature of unilateral deafness.

Though the radiologic examination showed normal mastoid cells in all cases, abnormalities of the internal auditory canal were encountered in 6 cases. In 5 cases the canal was so narrow that no space was available for the auditory nerve. Having normal embryology in mind, the impression is conceived of disturbances in the development of the petrous bone during the 2nd–3rd fetal month. In these 5 cases an osteoma of the bony internal canal is not a likely explanation in view of the age of the patients. In the case with a wider internal auditory canal there was no clinical evidence of any tumor of the cerebello-pontine angle. Explanation of this finding remained uncertain. The incidence of positive x-ray findings was in keeping with Everberg's observations referred to above.

ZUSAMMENFASSUNG

Das Gehör der Volksschulkinder in Helsinki wird in der 1., 3., 6. und 8. Klasse mit dem Audiometer geprüft. 1963–65 wurden unter 30 882 Schülern 28 Fälle gefunden, die auf einem Ohr vollständig taub waren, während das andere normal hörte. Die besprochene Untersuchung wurde an 27 Schülern mit einem Durchschnittsalter von 10 Jahren ausgeführt. Die Ätiologie konnte in 18 Fällen nicht ermittelt werden. Nach Mumps war ein Ohr in 3 Fällen taub geworden, nach Meningitis in 2 Fällen, nach Gehirnerschütterung in 2 Fällen, nach Masern in einem Fall und in einem Fall war die Mutter im Anfang der Schwangerschaft an Röteln erkrankt. Bei der Elektronystagmographie hatten 12 Patienten einen völlig normalen Vestibularisbefund, 4 Patienten wiesen eine beträchtliche Herabsetzung der Labyrintherregbarkeit der beiden Ohren auf, 4 Patienten hatten denselben Befund nur in dem betroffenen Ohr. Vier der Untersuchten hatten einen vollständigen Vestibularisausfall (vestibuläre Areflexie). Meatus acusticus internus war röntgenologisch in 5 Fällen im tauben Ohr enger und schlecht ersichtlich, dagegen war er in einem Fall weiter als im gesunden Ohr. Die röntgenologischen Veränderungen waren jedes Mal in Fällen vorhanden, wo die Ätiologie der Taubheit unbekannt war.

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explain the poorly developed internal auditory canal on the basis of labyrinthitis and osseous obliteration.

Antibody determinations for mumps were made in 10 cases, the titres are shown in Table 5 The highest titre occurred in a girl whose unilateral deafness was detected during the first school year and who developed mumps during the second year. In this case, the cause of deafness was not known. Only one of the 10 children examined had lost hearing in one ear in connection with mumps seven years before the examination concerned The titre in this case was 1/8.

DISCUSSION

Unilateral deafness detected or confirmed by hearing tests will always upset the child's parents to some degree, especially when they are told that there is no treatment for the ailment The question of its cause then arises. The literature shows that opinions vary widely: Everberg attributed deafness to mumps in 5 cases out of 122 (4 per cent) whereas in Lehnhardt's series the corresponding figure was 68 per cent. The former (1957) estimated that four-fifths of all cases of mumps deafness were unilateral and the incidence of deafness as a complication of mumps about 0 05 per thousand Vuori, Lahikainen & Peltonen (1962) studied a material consisting of 298 servicemen treated for mumps Sensory-neural hearing loss occurred in 13 patients (4.4 ± 1.2 per cent) Hearing became completely normal in 6 cases, almost normal in 6 and in only one patient did permanent unilateral deafness develop On the basis of their series, Vuori and his co-workers stated that while sensory-neural hearing loss in connection with mumps is not rare, it has no connection with mumps-induced meningitis They estimated the incidence of deafness at one per 200,000—exactly the same ratio as reported by Everberg In disagreement with Lehnardt the present authors doubt the value of the complement fixation test for mumps as an objective criterion of mumps deafness many years after the appearance of deafness

Any other virus disease can be considered as a possible cause of unilateral deafness, but the role of virus diseases is of speculative nature rather than proved (Rossberg, 1961) Bari & Lundström (1965) had a series of 752 cases with severe hearing impairment The incidence of maternal rubella was 12 per cent The audiograms of rubella-deafened children had a typical asymmetrical appearance, the curves being flat and the loss sometimes unilateral Vestibular function was usually normal Though rubella was first known to cause cataract in the children of mothers who had acquired rubella during the first trimester of pregnancy later reports have revealed that deafness is the most important complication of maternal rubella This series shows that deafness can also be unilateral

Our electronystagmographic findings were largely consistent with those of Pascher but differed greatly from the results of Everberg and Lehnhardt

TEDDY BEAR SCREENING AUDIOMETRY FOR BABIES

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For the early detection of hearing disorders—particularly in "at risk" children—a screening procedure using teddy bears containing loud speakers emitting worble tones has proved most efficient in children between the ages of 6 and 15 months.

Two years ago we started to test very young children using K. P. Murphy's technique of separating two head phones within the visual field of the child, introducing pure tones alternately in each phone.[1]

The technique is based upon the primitive acoustic reflex resulting in coordinated eye and head movements towards the source of the sound stimuli.

We determined after a few months of experimentation that pure tones were not as reliable as worble tones in free field testing. First, pure tones produce standing waves and second, they do not attract the attention of the child as readily as worble tones. Instead of using head phones we installed small loud speakers in the stomachs of two identical teddy bears, each of them provided with a button on the back so that the examiner could deliberately transmit the worble tones to either bear by pressing either button. There should be no click at the initiation of the tone. The most reliable results are obtained when the child is between 6 and 15 months of age (Fig. 1).

Screening Technique

(1) The child is comfortably placed on the lap of its mother or nurse.

(2) When the child is at ease, two teddy bears are held together in front of the child at a distance of about 40 cm (15 inches).

(3) The audiometer is set at a tone of 1000 cps frequency—modulated 5 per cent (2 hz) at an intensity of 40 dB.

(4) The bears are slowly moved apart from each other in a half circle and the child's eyes instinctively follow one of the bears. Then the examiner presses the button on the back of the other bear to produce the worble tone. If the child hears normally, his eyes will immediately turn to the "talking" bear or he may point to it (Fig. 2).

(5) The procedure is repeated at an intensity of 30 dB.

(6) The child is then tested with worble tones of 4000 and 250 cps at 30 dB.

[1] Personal communication in June 1963 from K. P. Murphy, Ph.D., the Nuffield Audiology Unit at Reading, England.

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EXPERIMENTAL PRESSURE VARIATIONS IN THE MEMBRANOUS LABYRINTH OF THE FROG

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Observation of the perilymphatic and endolymphatic membranes at operation on the labyrinth of the frog indicated a small or nonexisting pressure gradient between endolymph and perilymph A method for instillation of fluid into the labyrinth was described together with a method for measuring the hydrostatic endolymphatic pressure as a function of the amount of fluid instilled into it A linear relationship between the amount of fluid added to the endolymphatic labyrinth and its resulting hydrostatic pressure was found both at instillation of fluid and removal from the labyrinth indicating the presence of elastic properties within the endolymphatic membranes After a positive hydrostatic pressure had been applied to the endolymphatic labyrinth, the restoring of normal pressure within it and the mechanism for this restoring was studied

In 1938 Hallpike & Cairns were able to present histologic data proving dilatation of the endolymphatic system in cases of Meniere's disease This finding has later been repeatedly confirmed and has been regarded as an indication that raised endolymphatic pressure is involved in the pathogenesis of this disease On the other hand, this idea has also been doubted (Wustrow & Borgowsky, 1960)

Although no conclusive proof of endolymphatic hydrostatic pressure influencing labyrinthine function has been presented, an increase of intra labyrinthine pressure has been discussed as a probable source of vertigo A compression of smaller vessels causing secondary anoxia on sensory nerve cells has been considered as well as a direct pressure effect on this tissue Deformation of the ampullas by herniation of the utricle causing stimulation of the sensory epithelium (Lindsay, 1960) may be another possible mechanism for releasing vertigo by pressure

In order to explain the sudden attacks of vertigo some authors have introduced the utriculo-saccular valve into the discussion A sudden opening

This investigation was supported by the Swedish Medical Research Council grant no F 01-3 B X

Read at the Xth International Reunion for Medicine and Surgery in Turin Italy June 1965

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Fig 1

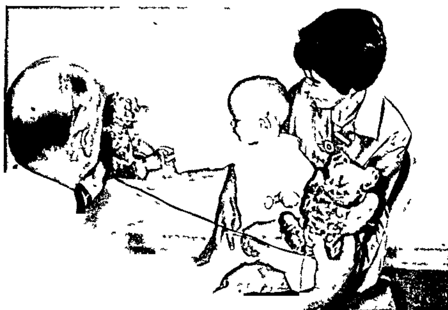


Fig 2

If the child reacts normally to the 3 frequencies, we may presume his hearing is normal, i e his hearing is adequate to the normal development of language

If the child does not react to the tones at 30 dB, the intensity may be raised in steps of 10 dB to a maximum of 70 dB, which is the maximum output of the small loud-speaker in each bear

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to withstand endolymphatic hypertension, (2) to present a method to measure the hydrostatic pressure in the labyrinthine endolymphatic space as a function of the amount of fluid instilled into it, and (3) to study the mechanism for restoring normal pressure within the labyrinth

A study of the vestibular activity as a function of the endolymphatic pressure will be accounted for in a later paper

METHODS AND MATERIAL

Frogs (Rana temporaria) were used in the experiments The results accounted for in this and the following paper are based on recordings from altogether 50 frogs and on observations at operations on about another 50 frogs

1 *Arrangements for instillation of fluid and for recording of pressure*

A pressure transducer, an air chamber a water manometer and a pipette were arranged as in Fig 1 The pressure transducer (EMT 34 Elema, Stockholm Sweden) had a volume displacement of 0 03 mm³/100 mm Hg This transducer is linear between 0 and 300 mm Hg The electromanometer (EMT 81) was a plug in unit in the recorder (Mingograf 81, Elema) The air chamber was made of glass 1 cm³ large and filled with air bordering on a vertical fluid surface In order to reduce thermical influence the air chamber – pressure transducer system (APT system) was lodged in a "foam plastic box By means of a syringe the water manometer could be given

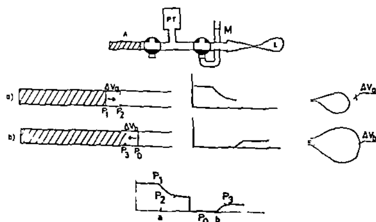


Fig. 1 Upper part principle arrangements of the air chamber (*A*) the pressure transducer (*PT*) the manometer (*M*) and the stopcocks for connections with the labyrinth (*L*)

Middle part (*a*) the relation between pressures (P_1–P_2) and the volume displacement (ΔV_a) at inflow to the labyrinth (*b*) corresponding relations at outflow (P_0 P_3 resp ΔV_b)

Lower part full line indicates the pressure within the APT system (the pressure recorded) dotted line indicates the pressure within the labyrinth at inflow (*a*) and at outflow (*b*)

of this valve might allow a hypertension in the lower portion to reach the upper portion of the labyrinth rather rapidly, thereby causing a sudden onset of vertigo (Williams, 1952; Altmann, 1955).

According to the recent hypotheses put forward by Lawrence & McCabe (1959) and later also by Schuknecht (1963) the attacks of vertigo are explained by sudden ruptures of the endolymphatic sacs, allowing endolymph to mix with perilymph and also causing collapses of various parts of the membranous labyrinth. Most of the above-mentioned hypotheses are based on anatomical findings at operations or histologic studies on patients with *Ménière's disease*.

Some experimental studies from which deduction could be drawn as to the relation between endolymphatic pressure and vestibular function have also been made.

Wittmaack (1956) and Mygind (1952) could vary the intralabyrinthine pressure by application of solutions of different saturation to the middle ear in animals and studied the effect of such procedures on vestibular function. These authors did not, however, measure the pressure manometrically.

With the aid of a mechanical model Tonndorf & van Bergeijk (1958) showed that the cupula deflection caused by an acting force in the system used was reduced at increased hydrostatic pressure in a portion corresponding to the utricle.

Aubry, Pialoux & Burgeat (1964) recorded pressure within the endolymph and found a rise of pressure at acoustic stimulation.

Inoue (1959), perfusing guinea-pig labyrinths to study the effect of different ions on nystagmus movements, used a perfusion pressure of 5 cm H_2O and did not at an adequate potassium level find any depression of the normal vestibular function except transitory nystagmus jerks at the beginning.

Some experimental data may be mentioned in this connection although derived from studying cochlear microphonics on increase of endolymphatic pressure. McCabe & Wolsk (1961) found a decrease of cochlear microphonics at increase of the endolymphatic pressure.

As to the original pressure levels in the endolymphatic and perilymphatic spaces of the cochlea, Weille *et al.* (1958, 1961) found indications of a greater perilymphatic than endolymphatic pressure. The results were, however, regarded as not conclusive by the authors themselves.

Sala, Giacomelli & Molinari (1965) made a histological study of an initial collapse and a following distension of the endolymphatic space of the guinea pig after application of saturated sodium chloride solution on the round window. They also found changes in DC levels and in spontaneous and induced vestibular activity after such applications.

Thus, so far no attempt has been made to study the vestibular activity at experimental increase of a recorded endolymphatic pressure.

The aim of the present paper is (1) to study the ability of the labyrinth

to withstand endolymphatic hypertension (2) to present a method to measure the hydrostatic pressure in the labyrinthine endolymphatic space as a function of the amount of fluid instilled into it, and (3) to study the mechanism for restoring normal pressure within the labyrinth

A study of the vestibular activity as a function of the endolymphatic pressure will be accounted for in a later paper

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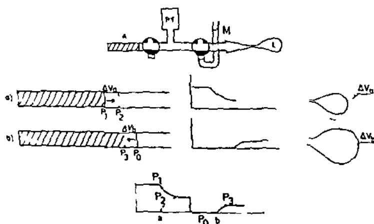


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any suitable pressure and these pressures could be applied to the APT system which then, disconnected from the water manometer, could be connected to the labyrinth. The pipette was a specially made glass capillary with a tip diameter roughly varying between 90 and 60 mikrons Its flexible connection with the APT system was made of glass, by which the volume displacement in the connecting system was greatly reduced

2. *Calibration*

For determining the order of duration for equilibration of a pressure difference in the APT system and a system connected to the tip of the pipette, the pressure fall from +3 5 cm H_2O to the zero level was recorded when the tip was placed just below a fluid surface in a large vessel The pressure fall time (from 0 9 to 0 1 of the initial pressure difference) was found to be 12–15 secs (depending on diameters of different pipettes) When the air chamber was disconnected the pressure fall time was 0 2 sec The volume displacement of the APT system was determined by applying different pressures to the system and then allowing fluid to leave the APT system and pass into a calibrated glass pipette made for blood counting while a simultaneous recording of the corresponding decrease in pressure was made The relation between the volume that reached the calibrated pipette and the meanwhile recorded decrease in pressure gave this APT system the volume displacement 0 9 $mm^3/cm\ H_2O$

3 *Types of preparations*

Curarized frogs were operated on in three different ways as shown in Fig 2

(A) The frogs were pinned to an operating table that could turn the frog upside down From the ventral side parts of the saccule and the ampullas of the lateral and of the anterior vertical canal were exposed From the dorsal side the posterior vertical canal was exposed and opened and a glass capillary was introduced in the direction of its non-ampullar end The tightening around the pipette was carried out with ligatures of human hair The portion of the canal behind the pipette was ligated in a similar way It was checked that no leakage took place from the ligated ends of the sectioned canal This technique thus permitted a direct visual study of the saccule through the microscope at instillation of fluid into the membranous labyrinth

(B) The roof of the skull in the region of the cerebellum was removed and the opening of the endolymphatic duct into the cranial cavity could thus be inspected The posterior vertical canal was opened and a pipette was introduced as in operation type A This preparation was used to study the patency of the endolymphatic duct before and after obstruction of its opening into the cranial cavity

(C) Preparations being combinations of A and B were also used When the endolymphatic pressure was increased in such preparations both the

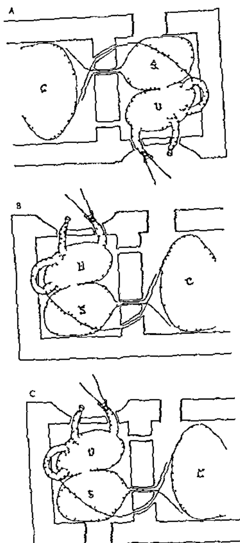


FIG. 2. The three different types of operation. The utricle (*U*), the saccule (*S*), and the brain (*C*). See text.

saccule and the endocranial opening of the endolymphatic duct could be observed.

4. *Methods for potassium and sodium determination*

The potassium and sodium concentrations in endolymph and perilymph were determined by means of micro flame photometry. The method, which is a modification by one of us (Johansson) of that described by Müller (1958) admits of quantitative determination of sodium and potassium in small volumes (10^{-4} mm^3). A known amount of the fluid to test is applied to the top of a platinum wire. This is then placed in a flame and the

any suitable pressure and these pressures could be applied to the APT system which then, disconnected from the water manometer, could be connected to the labyrinth. The pipette was a specially made glass capillary with a tip diameter roughly varying between 90 and 60 mikrons. Its flexible connection with the APT system was made of glass, by which the volume displacement in the connecting system was greatly reduced.

2. *Calibration*

For determining the order of duration for equilibration of a pressure difference in the APT system and a system connected to the tip of the pipette, the pressure fall from +3.5 cm H_2O to the zero level was recorded when the tip was placed just below a fluid surface in a large vessel. The pressure fall time (from 0.9 to 0.1 of the initial pressure difference) was found to be 12–15 secs (depending on diameters of different pipettes). When the air chamber was disconnected the pressure fall time was 0.2 sec. The volume displacement of the APT system was determined by applying different pressures to the system and then allowing fluid to leave the APT system and pass into a calibrated glass pipette made for blood counting while a simultaneous recording of the corresponding decrease in pressure was made. The relation between the volume that reached the calibrated pipette and the meanwhile recorded decrease in pressure gave this APT system the volume displacement 0.9 mm^3/cm H_2O.

3. *Types of preparations*

Curarized frogs were operated on in three different ways as shown in Fig. 2.

(A) The frogs were pinned to an operating table that could turn the frog upside down. From the ventral side parts of the saccule and the ampullas of the lateral and of the anterior vertical canal were exposed. From the dorsal side the posterior vertical canal was exposed and opened and a glass capillary was introduced in the direction of its non-ampullar end. The tightening around the pipette was carried out with ligatures of human hair. The portion of the canal behind the pipette was ligated in a similar way. It was checked that no leakage took place from the ligated ends of the sectioned canal. This technique thus permitted a direct visual study of the saccule through the microscope at instillation of fluid into the membranous labyrinth.

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Fig 3

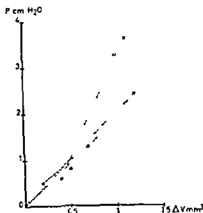


Fig 4

Fig 3 Original pressure recording at equilibration in pressure between the APT system and the labyrinth corresponding to the lower part in Fig 1

Fig 4 Intralabyrinthine pressure (p) as a function of amount of added fluid (ΔV) in three repeated experiments in the same labyrinth × values after inflow (P_2) and O values after outflow (P_3)

pressures rarely higher than 3.5–5 cm H_2O These pressures could be applied repeatedly without visible or recordable signs of membrane rupture

IV *a* Pressure grams from six frogs using endolymph like fluid were made When the stopcock between the APT system at overpressure (P_1) and the labyrinth at atmospheric pressure was opened, a distension of the saccule and frequently also a turbulence in the otoconia could be observed during about 1–3 sec During that period of time the recorded pressure showed a rapid decrease with a slope of an exponential character reaching a fairly stabilized level of pressure (P_2) (Fig 3 left part) In this way the amount of fluid (ΔV_a) instilled into the labyrinth as well as the increase of pressure (P_2) caused by the rapid addition of this amount of fluid to the labyrinth could be determined by measuring the rapid decrease in pressure (P_1 P_2) During the following period the pressure frequently tended to decrease following an exponential curve of considerably less however varying steepness

IV *b* The labyrinth was then (after about 30 sec) connected to the APT system after the latter, separated from the labyrinth for some seconds, had been adjusted to zero pressure (P_0) We then observed fluid leaving the distended saccule and also a diminishing of the saccule Meanwhile the pressure within the APT system increased and reached a stabilized level well above the zero level (P_3) (Fig 3 right part)

This type of experiment thus furnished data for plotting increase of pressure (P) against increase of volume (ΔV) both at increasing and at decreasing volumes of the labyrinth In some experiments the fall in pressure after P_2 was reached indicated that the labyrinth was somehow losing

total emission elicited by the potassium is recorded by means of a photomultiplier and an integrator unit.

This method was used also to determine the potassium concentration in perilymph after distension of the membranous labyrinth. In these experiments frog-Ringer was used for instillation in order to avoid potassium contamination from the pipette at its application into the semicircular canal. Perilymph from the vicinity of the anterior branch of the vestibular nerve close to the saccule was sucked into small, carefully cleaned glass capillaries and thus prevented from desiccation.

5. *Fluid used for instillation into the labyrinth*

For instillation into the labyrinth different kinds of fluid were used. In the first pilot experiments ordinary tap water, later frog-Ringer (sodium 110.3, potassium 4.3, calcium 1.4 and chlorides 116 mEq/l). After determination of the potassium level of the endolymphatic fluid, however, a solution intended to be more like the original endolymph of the frog in respect of the contents of potassium (sodium 25, potassium 136 and chlorides 161 mEq/l) was used in most experiments. The reason why this last type of fluid was not used during the whole series of experiments was our ambition to record ampullar nerve activity as well. We soon realized that small amounts of potassium solution trickling from the pipette at its application to the canal could depolarize the nerve enough to jeopardize our recording of the nerve activity.

We could, however, subsequently use endolymph-like fluid again when improved technique made it possible to protect the nerve from this potassium-rich fluid and when, in addition, we had found it possible to regain the activity of the nerve by irrigation with Ringer's solution.

RESULTS

I. The membranous labyrinth was observed visually during the surgical approach. When the bony perilabyrinthine capsule was removed, the perilymphatic wall could be seen bulging somewhat outwards and regaining its shape after having been slightly compressed by some instrument. Sometimes it could be seen moving in pace with the heartbeats. When the membrane was penetrated and the perilymphatic fluid sucked away the saccule seemed to lose its shape and become flatter.

II. As has been found in other species, also the frog's endolymph is rich in potassium and poor in sodium. As regards potassium the concentrations 143, 137 and 130 mEq/l were found in three experiments, while the sodium concentrations were about 10 mEq/l.

III. By applying different pressures to the APT system and connecting it to the labyrinth while simultaneously observing the labyrinth in a microscope, we found that the labyrinth (sacculus) ruptured at pressures exceeding 5–8 cm H_2O. For that reason most experiments were made using

Knowing the relation between pressure (P) and added volume (ΔV) in the APT system the amount of fluid escape from the labyrinth through the endolymphatic duct or the membranes or via the vessels could then be roughly estimated in such experiments. This escape, however, was rather slow and varied between 0.1 and 1.4 mm^3/minute.

VIII. Using the operations of types B and C, made to allow simultaneous observations of the endocranial opening of the endolymphatic duct and the saccule, attempts were made to correlate the escape of fluid from the labyrinth to outflow via the endolymphatic duct.

In this type of experiments the fluid for installation was coloured by addition of trypan blue or methylene blue. In some few experiments fluid could be seen entering the cranial cavity via the endolymphatic duct. In most experiments, however, no trace of any fluid leaving the labyrinth that way could be seen in spite of simultaneous reduction of the volume of the saccule and decrease of pressure. In some of these experiments the endolymphatic duct was even blocked by a latex plug forced into its endocranial opening. Instead a certain colouring of the capillaries in the vicinity of the endolymphatic walls could be seen as well as a colouring of the sensory epithelia and the nerves indicating fluid uptake in the vessels without any signs of colour in the perilymphatic space. Thus two possible ways for the fluid to escape could be established: via the endolymphatic duct and via the vessels.

IX. Regarding a third possible route for escape of fluid from the distended labyrinth—through the membranes—efforts were made to reveal a possible leakage of potassium into the perilymphatic space. To avoid a possible contamination by potassium from the pipette frog Ringer was used for instillation. These experiments are still too few to admit of any definite conclusion, but in 7 out of 8 experiments low potassium values were found in the perilymph after repeated labyrinthine distension while in the eighth experiment a slight increase was found.

DISCUSSION AND CONCLUSION

The findings here accounted for will be discussed together with the findings in a following paper on vestibular activity at experimental variations of endolymphatic pressure.

The labyrinths of frogs were exposed and observed at application of different endolymphatic pressures simultaneously recorded.

1. A loss of bulging as well as a flattening of the saccule when perilymphatic fluid was removed indicated a rather small or nonexisting pressure gradient between endolymph and perilymph.

2. High potassium and low sodium concentrations were found within the endolymph of the frog.

3. When a positive pressure gradient between endolymphatic and perilymphatic space of more than 5–8 cm H_2O was applied the labyrinth fre-

fluid (ΔV_c). This loss could be determined by the decrease in pressure during that period and was taken into consideration when the addition in volume (ΔV_a–ΔV_c–ΔV_b) still present after the outflow of (ΔV_b) causing the pressure P_3 was calculated

In Fig 4 is plotted the increase in intralabyrinthine pressure (P) against the amount of fluid (ΔV) added to the endolymphatic space at three repeated experiments on the same labyrinth

The values achieved in this type of experiment indicate that the pressure within the membranous labyrinth *is a roughly linear function of the amount* of fluid (ΔV) added to it

V In another type of procedure on three frogs fluid was stepwise added to the labyrinth and then stepwise removed from it while the resulting pressure was recorded Pressure plotted against added fluid again revealed *a linear relationship between* ΔV *and* P *found in the previous type of experiments*

VI. In some few experiments—when exposing the labyrinth to an overpressure—were no signs of any intrasaccular injection of fluid Only a small deviation of the saccule when it was pushed aside a little by a distended utricle was observed

In these instances the pressure recording also indicated a much smaller inflow of fluid to the labyrinth Such results were interpreted as being due to an obstruction of the utriculo-saccular connection In some of these cases the instilled fluid was coloured (see later) and the restriction of colour to the upper portion of the labyrinth could be seen

VII In the next type of experiment the intralabyrinthine pressure after instillation of fluid was followed for a somewhat longer period of time

In experiments where only the utricle was dilated by the fluid the pressure level reached after the inflow of the labyrinth was as a rule quite steady and stayed steady as long as the pressure in each experiments was recorded (from half a minute to several minutes) This indicates that the membranes of the utricle do not allow any passage of fluid at the hydrostatic pressure used—or if such passage does take place—it must be too small to be revealed by our method

On the other hand, in the more common situations when also the saccule was affected by the instilled fluid the pressure frequently showed an exponential decrease to the zero-level of varying steepness In 16 experiments on 4 frogs—out of 28 experiments on 8 frogs in which the endolymph-like fluid was used—there was no significant decrease in pressure recorded after the stabilized level was reached In the remaining 12 experiments on 6 frogs there was however, a definite decrease in pressure

Simultaneous observations of the saccule showed a reduction in size of the saccule corresponding to the recorded decrease in pressure This indicated that the main reason for decrease of pressure within the labyrinth was due to a loss of fluid and not which could have been anticipated if we had been unable to observe the labyrinth—due to a loss in elasticity

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2 High potassium and low sodium concentrations were found within the endolymph of the frog

3 When a positive pressure gradient between endolymphatic and peri lymphatic space of more than 5 8 cm H O was applied the labyrinth fre

quently ruptured and this rupture frequently affected the membranes of the saccule

4 The hydrostatic pressure within the endolymphatic labyrinth is an almost linear function of the amount of fluid added to it After application of an overpressure to the endolymphatic space an elasticity within the walls of the membranous labyrinth tends to prevent this pressure from being reduced to zero until the instilled amount of fluid has left the labyrinth

5 In some experiments an indication of obstruction in the utriculo saccular connection was found

6 After application of a positive pressure inside the membranous labyrinth the pressure recording follows an exponential decay curve of varying but often very moderate steepness indicating some escape of fluid from the labyrinth in at least some of the experiments

7 In some experiments an escape of fluid from the membranous labyrinth at overpressure took place *via the endolymphatic duct In others no* such escape was found

8 An escape of fluid from the labyrinth via capillaries was made probable by using coloured fluid for instillation

9 Unfinished experiments on the potassium level in the perilymph after *distensions of the labyrinth indicated that these ions did not* freely leave the endolymphatic space through its walls even at hydrostatic pressures large enough to cause considerable dilatations of the labyrinth

ZUSAMMENFASSUNG

Beobachtungen der perilymphatischen und endolymphatischen Membrane bei Operationen am Froschlabyrinth erwiesen einen kleinen oder nicht vorhandenen Druckgradient zwischen Endolymphe und Perilymphe Zusammen mit einer *Methode zur Instillation von Flussigkeit in das Labyrinth wird eine* Methode zur Bestimmung des endolymphatischen hydrostatischen Druckes als eine Funktion der Menge instillierter Flussigkeit beschrieben Ein lineares Verhaltnis zwischen der Flussigkeitsmenge die dem endolymphatischen Labyrinth zugefuhrt wurde und dem erhaltenen hydrostatischen Druck konnte nachgewiesen werden und zwar sowohl bei der Instillation der Flussigkeit als auch bei der Entleerung des Labyrinths Diese Resultate deuten auf elastische Eigenschaften innerhalb der endolymphatischen Membrane hin Nachdem ein positiver hydrostatischer Druck auf *das endolymphatische* Labyrinth ausgeubt worden war wurde der Ruckgang auf einen normalen Druck und der hierfur verantwortliche Mechanismus studiert

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A NEW QUANTITATIVE ATAXIA TEST BATTERY[1,2]

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Pensacola, Fla., U.S.A.

From the U.S. Naval Aerospace Medical Institute, Pensacola

A new multi-dimensional quantitative ataxia test battery employing the "rail method" of testing was developed to assess more precisely than heretofore postural equilibrium-disequilibrium under unusual conditions and stresses such as rotating environments. Validity of the standardized test procedures in the laboratory, in the field, and in clinical situations was demonstrated, and present and future uses of the Test Battery in normals and auricular-involved individuals in vestibular research as well as in related research-clinical areas were outlined.

The disturbances of equilibrium while standing or walking are diagnostic signs with a long tradition of usefulness in clinical medicine. Many procedures have been proposed to quantify these disturbances (Alden, Horton & Caldwell, 1932, Babskii, Gurfinkel & Romel, 1952, Barbey, 1944, Beck, 1911–1912, Bruck, 1895, Bullard & Bracket, 1888, Collins & Howe, 1924, Fearing, 1925, Fleishman, 1962, Fleishman, Thomas & Munroe, 1961, Frisina, 1957, Fukuda, 1959, Grant, 1943, Head, 1920, Hellebrandt & Braun, 1939, Hellebrandt & Franseen, 1943, Henmon, 1919, Hertzberg, 1929, Hinsdale, 1887, James, 1882, Kreidl, 1892, Miles, 1922, Monrad-Krohn, 1938, Morton, 1911, Moss, 1932, Pieron, 1918, Ricaldoni, 1928, Romberg, 1853, Rosenfeld, 1918, Seashore, 1947, Skogland, 1942, Smith, 1963, Travis, 1944, 1945, Vaghini, 1961, Vazuka, 1962, Vernon *et al.*, 1959, Vierodt, 1862, Wapner & Witkin, 1950, Witkin & Wapner 1950, Worchel & Dallenbach, 1948, 1950) but almost as many have not stood the test of time. The procedures commonly used today, subjective estimates of disequilibrium, are valued mainly as rough screening tests to indicate lines of direction for more precise diagnostic study and, judging from the small investigative interest expressed in such tests, it must be assumed that they are adequate for all except special purposes.

Our interest in ataxia tests grew out of the fact that subjects exposed to the unusual inertial forces in a rotating environment initially experience ataxia then gradually adapt, and a quantitative measure of the time-course

[1] The opinions or conclusions contained in this report are those of the authors and do not necessarily reflect the view or endorsement of the Navy Department.

[2] This study was conducted under the sponsorship of the Office of Advanced Research and Technology, U.S. National Aeronautics and Space Administration Order No. R-93.

of this adaption was needed It is the purpose of this report to describe a new ataxia test battery with numerical scores, demonstrate its reliability and validity, and point out some of its uses in laboratory and clinic

All of the tests were carried out using "rails" (Beck, 1911–1912, Birren, 1945, Bruck, 1895, Callahan 1958, Courtney & Johnson, 1930, Cureton, 1951 Dunn, 1938, Davey, 1954, Fleishman, 1962, Fleishman, Thomas & Munroe, 1961, Frisina, 1957, Goetzinger, 1961, Graybiel *et al*, 1965, Guedry, Kennedy, Harris & Graybiel, 1964, Heath, 1942, 1943, 1944, Kreidl, 1892, Morsh 1937 Myklebust, 1946, Newsom, Brady & Goble, 1965, Seashore, 1947 Vernon *et al*, 1959, Whitney, 1937) with their advantages of flexibility in width and objectivity in scoring, i e, the subject either remained "on" or fell off ' The subject was required to remain upright with arms folded and stand or walk heel to toe as the case might be Well-fitting shoes with nonflexible soles and low heels were required

Only two measurements were made (1) the number of seconds the subject could 'stand and (2) the number of "steps' he could take without falling No attempt was made to grade variations in the amount of body sway A number of trials were given to increase reliability The test procedures described in Appendix A represent the end product of evolutionary development during which many variations of tests were tried and the various items subjected to statistical analysis Two versions of the test evolved a Long Version which utilized six rails of varying widths, and a Short Version which utilized only two of these rails

The Long Version serves the purpose of assessing the performance capabilities of extreme age groups (children and senior citizens) and certain clinical patients It offers the major advantage of establishing subtle individual differences in such samples

The Short Version as will be seen from our results serves ideally the purpose of assessing individual differences in normal subjects and fulfills the premium time saving requirement imposed by much repeated pre-, per- and post testing of subjects with no vestibular dysfunctioning, or with varying amounts of vestibular losses, who are exposed to unusual experimental situations

TEST BATTERY (LONG VERSION)

A total of 550 normal males, 11 labyrinthine defective males (L D's—college professors, graduates or near college graduates), and 158 females widely varying in age and occupational status comprise the samples tested with the Long Version of the Test Battery The samples include highly experienced Naval and Marine Corps test pilots aviators, Project Gemini applicants—one is new a Gemini Astronaut military flight surgeons,

Test Battery refers only to the three tests undertaken on the rails viz, Walk H T walking heel to-toe with eyes open) Stand E O (standing heel to toe with eyes open) and Stand E C (standing heel to-toe with eyes closed)

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The Short Version, as will be seen from our results, serves ideally the purpose of assessing individual differences in normal subjects and fulfills the premium time saving requirement imposed by much repeated pre-, per-, and post-testing of subjects with no vestibular dysfunctioning, or with varying amounts of vestibular losses, who are exposed to unusual experimental situations.

TEST BATTERY (LONG VERSION)[1]

A total of 550 normal males, 11 labyrinthine defective males (L.D.'s—college professors, graduates or near college graduates) and 158 females widely varying in age and occupational status comprise the samples tested with the Long Version of the Test Battery. The samples include highly experienced Naval and Marine Corps test pilots, aviators, Project Gemini applicants—one is now a Gemini Astronaut, military flight surgeons,

[1] Test Battery refers only to the three tests undertaken on the rails, viz., Walk H.T. (walking heel to toe with eyes open), Stand E.O. (standing heel to toe with eyes open) and Stand E.C. (standing heel-to-toe with eyes closed).

TABLE 1. *Test Battery (Long Version): means and standard deviations by age classification in samples of male[a] and female populations*

N	Age range	Walk H/T Test Mean	Walk H/T Test S.D.	Stand E/O Test Mean	Stand E/O Test S.D.	Stand E/C Test Mean	Stand E/C Test S.D.
Males							
32	13–16	51.3	5.36	469.2	61.09	190.0	89.15
124	17–42	54.8	4.53	483.1	59.15	203.7	98.61
9	43–50	56.7	4.08	457.4	88.78	150.4	98.01
4	51–53	54.5	5.50	416.3	92.19	120.8	70.97
7	54–66	45.3	9.11	322.1	139.01	101.7	67.88
Females							
28	14–16	51.5	4.26	489.6	41.71	225.8	69.08
112	17–42	51.3	4.66	486.2	54.49	232.3	91.52
7	43–50	46.6	6.61	475.6	33.95	196.1	107.24
2	51–53	43.0	1.00	320.0	32.00	49.5	1.50
9	54–67	41.0	10.34	296.8	140.73	90.7	77.78

[a] The samples here represented do not include 74 student military aviators and "Project Astronaut Candidates."

Naval and Marine Corps student aviators and "Project Astronaut Candidates" (Ambler & Berkshire, 1962), military officers and enlisted personnel, firemen, college professors, college students, senior citizens, clerical and technical medical staff, physicians, medical students, nurses, scientists, and high school students.

The Test Battery, the Classical Romberg Test (Romberg, 1853), and the Sharpened Romberg Test (SR) (Barbey, 1944) which were undertaken by these subjects are described fully in terms of materials, administration, and scoring procedures in Appendix A.

Normative data

Test Battery means and standard deviations by age classification in the samples of male and female populations are shown in Table 1. The ranges of scores observed in each sample and the percentile rankings are contained in Appendix B. There were marked individual differences in performance. The two standing tests appear to be more sensitive to age increase than is the Walk H/T test. *In males, standing test performances appear to decline significantly as early as age 43,* and Walk H/T performance appears to decline significantly at the later age of 54.

Reliability

Intra-test correlations (r's between best trial and second best trial) of Walk H/T ranged from 0.75 to 0.92, intra-test correlation of Stand E/O

and Stand E/C ranged from 0.83 to 0.96. Test-retest reliabilities ranged from moderate to high (r's of 0.57 to 0.96) over a period of seven successive test sessions in a group of twelve normal subjects.

Practice effects

Walk H/T performance plateaued at 9 per cent improvement on the fourth day. Stand E/O performance plateaued at 29 per cent improvement on the fourth day. Stand E/C performance plateaued at 9 per cent improvement on the fifth day.

Inter-test relationships

Correlations between Walk H/T and Stand E/O ranged from 0.37 to 0.69; correlations between Walk H/T and Stand E/C ranged from 0.13 to 0.48; correlations between Stand E/O and Stand E/C ranged from 0.41 to 0.61. It is apparent from these results that each test comprising the Test Battery relates only moderately to each other test and thereby suggests a nearly ideal distinctness desired in a battery of tests designed to measure complex performances referred to singularly as ataxia or postural equilibrium.

Height and weight influences

All correlations with height and weight (except in highly heterogeneous subjects) were very low or zero order and had negligible influences upon performance.

Validity

Labyrinthine defective group. The majority of this group scored at the 1st percentile on each of the tests. In this group virtually no improvement with extended practice was shown in their Stand E/C performances (only 3 per cent), whereas Walk H/T and Stand E/O performances typically improved rather markedly—70 per cent and 60 per cent, respectively, over seven daily retest periods.

Prediction of motion sickness susceptibility

In a small group of male subjects (N = 15) who were evaluated with regard to susceptibility to motion sickness by means of a motion sickness questionnaire, a boat ride, an exhaustive motion sickness arousing air ride and rotations on the Pensacola Slow Rotation Room (SRR) and on the Toronto Counter Rotating Platform (Graybiel & Johnson 1963), susceptibility to motion sickness was predicted to a moderate extent; correlations with the Test Battery ranged from 0.50 to 0.75.

Discriminatory power and limitations of the long version

Inter-correlations of performances by normals on each of the six rails disclosed that Rail 5 (3/4" wide) showed highest communality with the

TABLE 2 *Test Battery (Short Version) means and standard deviations by age classification in samples of male and female populations*

N	Age range	Walk H/T Test		Stand E/O Test		Stand E/C Test	
		Mean	S D	Mean	S D	Mean	S D
Males							
310	17–42	12.5	2.62	37.6	31.98	103.8	58.37
471	43–50	10.4	3.10	19.1	13.47	52.0	45.90
17	51–53	9.2	3.99	13.2	5.87	21.2	11.09
Females							
41	18–29	11.5	2.66	26.7	14.05	84.6	60.92
47	30–49	9.9	2.95	18.8	10.65	49.1	43.33
11	50–59	8.8	1.00	13.5	5.90	42.6	37.61

remaining rails in the case of Walk H/T and Stand E/O, and Rail 2 (3 1/4" wide) showed highest communality in the case of the Stand E/C test. Consequently, in the interest of economy we pilot-tested a large number of randomly selected miscellaneous normal subjects with the modified procedure of scoring the best three out of five trials. The Short Version of our Test Battery was derived utilizing these two rails.

TEST BATTERY (SHORT VERSION)

A total of 828 normal males, 10 of the L.D.'s tested previously on the Long Version, 17 male otoneurological patients, 99 normal females and 15 female otoneurological patients comprise the samples tested. The normals included experienced military aviators, Naval and Marine Corps student aviators and "Project Astronaut Candidates", flight surgeons, military officers, enlisted personnel, and military and civilian scientific, clerical and technical personnel.

The Test Battery (Short Version) and the Sharpened Romberg test were undertaken by all subjects, and in addition, many of the subjects undertook the Stand One Leg Eyes Closed test (SOLEC) (Beck, 1911–1912, Bruck, 1895, Worchel & Dallenbach, 1950), and the Walk Line Eyes Closed test (WALEC) (Monrad-Krohn, 1938, Vazuka, 1962). These are described fully in terms of materials, administration, and scoring procedures in Appendix A.

Normative data

Subjects tested to date ranged 17–59 years in age. As with the Long Version, there were marked individual differences in the capabilities tapped by the Short Version, and there was considerable overlap in the performances of older and younger individuals (Table 2). The ranges of scores observed

and the percentile equivalents are shown in Appendix C In the males tested, performance declined significantly in about the age range of 43 to 53 years

Intra test reliability

Intra test correlations (best trial with second best, best trial with third best and second best with third best) of Walk H/T scores ranged from 0 71 to 0 90, of Stand E/O scores from 0 89 to 0 96, and of Stand E/C scores from 0 82 to 0 96 Thus, performance on a given test utilizing a single rail, as opposed to utilizing six rails, duplicated the high reliability established for the Long Version

Test retest reliability

In a group of twelve normal male subjects in the age range 18–49 who undertook ten successive daily performances[1] on the Test Battery, test retest reliabilities, computed by correlations of Day 1 performance with mean performances on Days 2 through 10, were 0 40, 0 86, and 0 91 for Walk H/T Stand E/O, and Stand E/C respectively Other combinations of initial and early performances when correlated with later, practiced performances yielded virtually identical coefficients Substantial repeatability of standing test performances was apparent The lower reliability of Walk H/T performance reflects the more rapid rate of learning afforded both by the locomotor aspect of this test, and in turn, a more easily attained perfect score than was found on the standing tests Comparisons of Days 1 and 2 (combined) with Days 9 and 10 (combined) performances revealed 26 per cent improvement on Walk H/T, 77 per cent on Stand E/O, and 85 per cent on the Stand E/C test

Practice effects and effects of footwear upon highly practiced performance

In the group of twelve normal male subjects performances improved in almost linear fashion throughout the ten-day period although the improvements were relatively slight following the plateau points on the learning curve Plateaus in Walk H/T, Stand E/O, and Stand E/C performances were realized on the third fourth and fifth day, respectively The detrimental effects of wearing basketball shoes upon highly practiced standing test performances (obtained while the subjects wore street shoes) reached the extent of a 44 per cent decrease in Stand E/O performance and a 47 per cent decrease in Stand E C performance In marked contrast, Walk H T performance decreased a mere 6 per cent, indicating that the loss of stability due to basketball shoes was almost completely compensated for on Walk H T and very poorly compensated for on the two standing tests

[1] Two additional daily re tests were administered while subjects wore basketball shoes

Inter-test relationships

Correlations among the three distinct tests comprising the Short Version corresponded very nearly to those reported for the Long Version The correlations ranged from 0 19 to 0 51

Height and weight influences

The correlations with the Test Battery were very low, or zero order, and negligible for differentiation and prediction purposes—a finding in keeping with results on the Long Version.

Validity

The identification of individuals with auricular defects The mean performance scores of L D's, streptomycin-treated Meniere's patients, and clinical patients which included those showing postural vertigo, positional nystagmus, Meniere's, pseudo-Ménière's, and labyrinthitis were compared with the mean performance scores of an equivalent number of randomly sampled, age-matched normal, symptom-free, individuals In all instances, the performances of individuals with auricular involvement were significantly poorer than the performances of the normals

Relationships with threshold caloric responses

The performances of eleven symtom-free male individuals with below normal threshold caloric responses (> 35 0°C) were compared with the performances of eleven randomly selected normal male individuals with normal threshold caloric responses (36 0° to 36 6°C) Both Stand E/O and Stand E/C performances were identified with depressed semicircular canal sensitivity insofar as such sensitivity is reflected by caloric responses in the range of 35 0°C and below (02 level of confidence) Mean Walk H/T performances in the two groups were virtually identical

Identification of canal sickness susceptibility

In a sample of twenty normal male subjects the test performances of the ten most susceptible to canal sickness on the SRR were compared with the test performances of the ten remaining i e, least susceptible subjects Susceptibility in this instance was defined as a rank ordering of the twenty subjects in terms of the number of dial sequences completed during rotation and qualitative ratings by an observer (Kennedy & Graybiel, 1962) Generally, on all three tests the ten most susceptible subjects as a group attained higher performance scores than those attained by the least susceptible subjects To this extent, the Test Battery would appear to reflect sensitivity to canal sickness, which is a finding in parallel with predictability of motion sickness from Long Version performance

Effects of prolonged rotation in the Pensacola slow rotation room

Prerotation Test Battery performances were compared with postrotation performances in several groups of normal subjects who were rotated at 10 RPM for 12 days in the SRR (Graybiel *et al*, 1965) Post-testing occurred immediately upon cessation of rotation and in all instances severe declines in test performances were evidenced Daily retesting during the postrotation periods revealed complete recovery, within 24–72 hours, of all Test Battery performances except Stand E/C performances The visually influenced performances on the Walk H/T and Stand E/O test had not only recovered but had improved whereas the nonvisually-influenced Stand E/C performances proved more sensitive to the influences of prolonged rotation

Influences of moderate and severe sea conditions upon performance

In the Nova Scotia Experiment[1] twenty normal male subjects withstood a twenty eight hour ride on an ocean going tug in mid-winter during moderate and severe sea conditions between Nova Scotia and Newfoundland The performances of the lowest scoring subjects were hardly affected by the sea experience

Relationships with trampoline performance

From each of several successive classes of student aviators undertaking physical training in the U S Naval School, Pre-Flight, two to four men at the very top in terms of proficiency on the trampoline and two to four men at the very bottom in trampoline proficiency were selected for performance testing (Subjects were very carefully selected by Mr Joseph F Louder Physical Education Instructor, Naval School Pre Flight and Coach, Navy Starflights trampoline demonstration team) It was found that the top group on the trampoline scored higher on Walk H/T (01 confidence level) and Stand E/O (10 confidence level) than did the bottom group

Some relationships with several clinical type ataxia tests

Several individuals who undertook the Test Battery also took the following tests (described fully in Appendix A) Sharpened Romberg (SR), Stand One Leg Eyes Closed and Walk Line Eyes Closed The Test Battery performances of normal male subjects who scored perfectly on these clinical type tests were compared with the Test Battery performances of age-matched normal male subjects who had scored less than perfect on the clinical type ataxia tests Generally, results were in the direction of positive relationships between Test Battery scores and scores obtained on the ataxia tests

[1] In preparation for publication

Comparative difficulty in performing the Stand E/C test and the Sharpened Romberg test in relation to age

Quantitative comparisons of the two tests in terms of difficulty in samples of male subjects ($N=530$) and female subjects ($N=211$) in various age ranges revealed remarkable differences. Some 24 per cent to 92 per cent of the subjects scored perfectly on the first trial of the SR test, but only 3 per cent to 23.5 per cent of the subjects scored perfectly on the first trial of the Stand E/C test. Eighty-seven per cent of the younger subjects (ages 19–26) scored perfect first trials on the SR, and only 56 per cent of the older subjects (ages 43–53) did so. But greater still was the percentage differences in Stand E/C performance between the younger group and the older group —18 per cent perfect first trial scores in the younger group versus only 3.5 per cent perfect first trial scores in the older group. These findings reflect a mean age difference between the two groups of twenty-three years.

Influence of alcohol upon Test Battery and clinical-type ataxia test performances

As part of a larger study (Fregly, Bergstedt & Graybiel, 1965) which included positional alcohol nystagmus measurements and blood alcohol measurements, it was found that the SR test proved least sensitive to alcohol both in terms of decrement and recovery time, whereas the Test Battery proved most sensitive in terms of recovery time although it tended to equal the SOEC and WALEC in terms of the extent of performance decrement.

DISCUSSION

Our experience with the Test Battery has centered mainly around its use in measuring vestibular ataxia. It was found to be a reliable indicator *both of loss of vestibular function and disturbed function*. With regard to the former, our findings suggest that small loss (or suppression) of semicircular canal function in the presence of normal otolith function, as revealed by the counterrolling test, is sufficient to cause slight ataxia. This is supported by the results of Igarashi *et al.* (Igarashi, McLeod & Graybiel 1965), who produced ataxia in squirrel monkeys by the administration of streptomycin sulfate. Subsequent pathological studies revealed a significant loss of sensory epithelium of the cristae with little or no pathological changes in the maculae. The significance of these findings should be limited only to the probability that loss of semicircular canal function alone may lead to ataxia; the data are insufficient to evaluate fully the relative roles of both vestibular organs.

Further experience with the Test Battery is needed to determine its limitations and exploit its usefulness. Its adaptability readily can be made for either general or specific purposes.

In the laboratory, it would appear to have great value in measuring

adaptation in dynamic force environments, as our experiences with the Slow Rotation Room have shown (Bergstedt, 1965, Graybiel *et al* 1965, Guedry, Kennedy, Harris & Graybiel, 1964)

In the clinic, particularly otolaryngology, neurology, and geriatrics greater attention to finer, differential details of postural equilibrium functioning may facilitate diagnostic and treatment formulations

Awaiting all researchers who seek a fuller understanding of postural equilibrium functioning are such problems as elaborating the practical as well as theoretical significance of appreciable differences between a given individual's visual and nonvisual performance capabilities of differentiating more carefully locomotor and other types of ataxia from vestibular ataxia of clarifying the notion of an otolithic ataxia versus a semicircular canal ataxia of definitively measuring differences between dynamic" and static equilibrium and of delineating apparent differences between nature and nurture influences upon equilibration generally

Available vehicles for such research include the systematic study of such unusual individuals as congenitally and adventitiously blind persons with and without vestibular dysfunctioning, persons with unilateral and bilateral vestibular dysfunctioning ranging from minimal to "complete" persons with circumscribed neurological handicaps and disorders involving the vestibular pathways and apparently normal individuals with extraordinarily good postural equilibrium functioning Most desirable are longitudinal studies which systematically include vestibular evaluations as part of the complete medical evaluation (Harlan, Graybiel & Osborne, 1962 McFarland & Franzen 1944) and ideally the cross sectional and longitudinal vestibular functional testing of large numbers of individuals at all ages whose temporal bones will, eventually be made available for structural functional correlational analysis If in such studies the postural equilibrium evaluations are quantified then data processing would be facilitated considerably by modern computers

In conclusion the Test Battery may prove useful in the study of (1) the influences of sensory and sensory motor alterations or stresses (isolation, deprivation fatigue boredom suggestibility et cetera (Vernon *et al* 1959) (2) short and long term neuromuscular effects (including muscle atrophy) (3 zero G and sub-G environments including water immersion and rotating space vehicles (3) the influences of physiological aging and of physical fitness In the clinic one or the other version of the Test Battery may prove invaluable for the study of problems in otolaryngology neurology and geriatrics

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RÉSUMÉ

Une nouvelle série de test multi-dimensional quantitative d'ataxie a été développée utilisant la « méthode à rails » afin de déterminer plus précisément la posture équilibre-déséquilibre sous certaines conditions et sous des forces extraordinaires, comme un environment rotant. La validité de procédure de standardisation des test en laboratoire, en général et dans les situations cliniques a été démonstrée pour l'usage présent et future de ces tests sur des individus normaux et sur ceux impliqués auriculairement en recherches vestibulaires et aussi dans tout ce qui est la recherches clinique.

ZUSAMMENFASSUNG

Eine neue multidimensionale Testserie für quantitative Ataxie wurde entwickelt. Dabei wurde eine „Schienen-Methode" (Balancierschienen) benutzt, um genauere Resultate als bisher für das Gleichgewicht und Gleichgewichtsstörungen des Körpers in aufrechter Haltung unter ungewöhnlichen Bedingungen und Anspannungen — wie z. B. eine rotierende Umgebung — zu erzielen. Die Gültigkeit von Standardtest-Prozeduren im Laboratorium im allgemeinen und in klinischen Situationen wurde veranschaulicht. Gegenwärtige und zukünftige Anwendungen der Testserien bei normalen und bei auricular behafteten Personen in der vestibulären Forschung sowie in verwandten klinischen Forschungen wurden gezeigt.

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APPENDIX A Postural Equilibrium Tests and Clinical Type Ataxia Tests Apparatus Administration and Scoring Procedures

Apparatus[1]

Test Battery (Long Version)

Six rails of pine wood construction each 8 feet long and each superimposed on its 5 ,″ wide plywood base and each with width and height dimensions as follows Rail 1 2″, wide and 1 high (above base) Rail 2 2¹,″ wide and 1″ high Rail 3 1³/″ wide and 1″ high Rail 4 1¹/₄″ wide and 1″ high, Rail 5 ″ wide and 1″, high Rail 6 ,″ wide and 1¹/₂″ high The four widest rails are attached to the top of the base whereas the two narrowest rails are inserted within the base and held there by screws underneath to provide adequate support Rails 5 and 6 are , higher from the base than Rails 1 4 to prevent subjects from obtaining support from the base by means of over riding the feet Also to prevent splintering primarily of Rails 5 and 6 the top of each rail is covered by , thick Fiberglas attached by means of ordinary glue

A more durable version of the apparatus consists of a singular metal base (with the same dimensions as each wooden base) within which each of six metal rails (with sand blasted top surfaces and with dimensions identical with the wooden version) may be inserted readily by simple turning of two rigid securing hand screws Four pairs of set screws within the base permit leveling on uneven floors

[1] Utmost safety precaution is necessary on the part of the examiner to prevent possible injury of subjects from inadvertent falling

Test Battery (Short Version)

Rail No. 2 (2 1/4" wide, 30" long) and Rail No. 5 (3/4" wide, 8' long) of the Long Version (wood version or metal version) (Fig. 1 A) or a portable, foldable metal unit specific to the Short Version.

Method

Test Battery (Long Version)

The tests were performed with *shoes on.* Most male subjects wore a military or military-type shoe with relatively thick soles, whereas most female subjects wore relatively thin-soled flats. Prior to testing, all subjects read the following instructions:

Test Battery (Long Version)

Instructions

Test sequence

(*a*) Walking with eyes open on each of six rails of varying width.
(*b*) Standing with eyes open on each of the six rails.[1]
(*c*) Standing with eyes closed on each of the six rails.

Body position for all tests

(*a*) Body erect or nearly erect.
(*b*) Arms folded against chest.
(*c*) Feet in heel-to-toe position.
(*d*) Feet tandemly aligned.

Scoring

The *best two out of three* trials constitutes the scoring of each test.

(*a*) Walk H/T Test.—The first two steps, which are necessary for positioning *on the rail, are not scored. A trial begins when the third step is taken.*

(*b*) Stand E/O Test.—Timing begins as soon as correct position on the rail is assumed.

(*c*) Stand E/C Test.—You may take unlimited time for positioning yourself on the rail first with your eyes open. Timing will begin as soon as you close your eyes. Examiner will observe your eyes carefully, so that signalling the examiner is unnecessary.

General

As there does not appear to be any single "best method," you must develop (rapidly) your own techniques. You may position your head up or down and/or forward or backward; you may lean forward or backward slightly if you do not prefer a perfectly erect position; *between trials* alternation of the feet is permissible; you may place more weight on your front foot than on your rear foot or vice versa, or you may distribute your weight equally. However, a stooping position should be avoided.

[1] Normal subjects began on Rail 3, and if a perfect score was attained, subject was credited with perfect performances on Rails 1 and 2. If score on Rail 3 was less than perfect, testing was undertaken on Rail 2 (and Rail 1 if necessary) and upon completion subject proceeded to Rail 4.

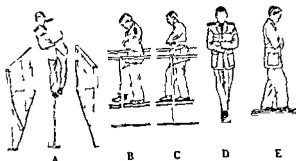


Fig 1 A Test Battery (Short Version) A–B Walk H/T Test (on ³/₄" wide rail), C Stand F O Test (on ³/₄" wide rail) and D E Stand E/C Test (on 2¹/₄" wide rail)

Originally published in AEROSPACE MEDICINE, Vol 36 No 12 Dec 1965 p 1165 as Fig A1

After subjects read the instructions the examiner demonstrated all procedures and attempted to answer all questions raised about the manner of performing The brief demonstration included illustrations of correct versus incorrect body and foot positions two or three demonstrations of walking one or more rails with emphasis that speed of walking should be considered secondary to negotiating the rails, and one or more demonstrations of appropriate positions for standing with eyes open and closed The importance of maintaining the tandem heel to toe position was reemphasized as often as necessary Subjects were requested to avoid signalling the examiner upon closing the eyes to minimize losses of assumed position(s) on the rail(s)

Not included on the score sheet were the 'false starts' defined as inadequate initial positioning on the rail leading to immediate loss of equilibrium on any trial or a low time score (usually two or three seconds) not in keeping with a given subject's generally higher level of performance (Faulty techniques may be distinguished from inability even by inexperienced examiners) The scoring procedures were as follows

Scoring Procedures

Walk H T Test

(*a*) Each correct step is scored as one (step)

(*b*) Maximum trial score equals five (steps)

(*c*) Maximum rail score equals ten (steps) or total of the two best trials

(*d*) Maximum test score equals 60 (steps) the sum of all six rail scores

Stand E O Test

(*a*) Timing to the nearest second begins when subject assumes correct and balanced position on the rail and timing ends at 60 seconds or when subject violates his position or falls off the rail

(*b*) Maximum trial score equals 60 (seconds)

(*c*) Maximum rail score equals 120 (seconds) the sum of the two best trials

(*d*) Maximum test score equals 720 (seconds) the sum of all six rail scores

Stand E C Test

(*a*) Timing begins as soon as positioned subject closes his eyes and timing ends at 60 seconds or when subject violates his position or opens his eyes, or falls off the rail

(*b*) Maximum trial score equals 60 (seconds)
(*c*) Maximum rail score equals 120 (seconds), the sum of the two best trials
(*d*) Maximum test score equals 720 (seconds), the sum of all six rail scores

Classical and Sharpened Romberg procedures

Prior to undertaking the Test Battery, subjects were administered one trial of the classical Romberg test with eyes closed. Subjects who failed to stand the required 60 seconds were then administered one trial of the Classical Romberg Test with eyes open. These subjects then were administered one trial in the Sharpened Romberg position[1] with eyes closed. Subjects who failed to stand the required 60 seconds then attempted to stand in the Sharpened Romberg position for a period of 60 seconds with eyes open.

Test Battery (Short Version)

As with the Long Version, the tests were performed with *shoes on*. Again most of the males wore a military or military type shoe, whereas most female subjects wore relatively thin soled flats. Prior to testing, all subjects read the following instruction sheet.

Test Battery (Short Version)

Instructions

Test sequence
(*a*) Walking with eyes open on a 3/4" wide rail
(*b*) Standing with eyes open on a 3/4" wide rail
(*c*) Standing with eyes closed on a 2 1/4" wide rail

Body position for all tests
(*a*) Body erect or nearly erect
(*b*) Arms folded against chest
(*c*) Feet in heel to toe position
(*d*) Feet tandemly aligned

Scoring

The *best three out of five* trials constitute the scoring procedure.

(*a*) Walk H.T. Test.—The first two steps which are necessary for positioning on the rail are not scored. A trial begins when the third step is taken.

(*b*) Stand E.O. Test.—Timing begins as soon as correct position on the rail is assumed.

(*c*) Stand E.C. Test.—You may take unlimited time for positioning yourself on the rail first with your eyes open. Timing will begin as soon as you close your eyes. Examiner will observe you carefully so that signalling the examiner is unnecessary.

General

As there does not appear to be any single "best method" you must develop (rapidly) your own techniques. You may position your head up or down and/or

[1] The Sharpened Romberg position refers to the following: Subject attempts standing on floor for 60 seconds in arms folded against chest, feet tandemly aligned and heel to toe.

forward or backward, you may lean forward or backward slightly if you do not prefer a perfectly erect position, *between trials* alternation of the feet is permissible, you may place more weight on your front foot than on your rear foot or vice versa or you may distribute your weight equally However, a stooping position should be avoided

As with the Long Version, after subject read instructions the examiner demonstrated all procedures and answered all questions raised about the performance procedures Examiner gave two or three demonstrations of walking the ³/₄ wide rail and one or two demonstrations of standing on each of the two rails The scoring procedures were as follows

Scoring Procedures

Walk H/T Test

(*a*) Each correct step is scored as one (step)
(*b*) Maximum trial score equals five (steps)
(*c*) Maximum test score equals fifteen (steps), the sum of the three best trials

Stand E/O Test

(*a*) Timing to the nearest second begins when subject assumes correct and balanced position on the rail, and timing ends at 60 seconds, or when subject violates his position or falls off the rail
(*b*) Maximum trial score equals 60 (seconds)
(*c*) Maximum test score equals 180 (seconds), the sum of the three best trials

Stand E C Test

(*a*) Timing begins as soon as positioned subject closes his eyes and timing ends at 60 seconds or when subject violates his position or opens his eyes or falls off the rail
(*b*) Maximum trial score equals 60 (seconds)
(*c*) Maximum test score equals 180 (seconds), the sum of the three best trials

Sharpened Romberg Test (SR)[1]

All subjects prior to undertaking the Test Battery undertook the SR test Subjects who failed to stand for the required period of 60 seconds on the first trial were administered a second trial Subjects who failed to stand 60 seconds on the second *trial were administered a third trial before* proceeding with the Walk H T Test Subjects who failed to stand 60 seconds on the third trial were administered an additional (fourth) trial upon their completion of their Stand E C Test

SR performance was scored as follows A perfect score of 60 seconds on the first trial was weighted 4 and a score of 240 (60 × 4) was assigned, a perfect score on the second trial was weighted 3, and 180 (60 × 3) plus the number of seconds stood on the first trial become the assigned test score a perfect score on the third trial was weighted 2 and 120 (60 × 2) plus the number of seconds

[1] Indicates standing in the Sharpened Romberg position with eyes closed for a maximum of four trials

stood on the first two trials became the assigned test score, with subjects requiring a fourth trial, the total number of seconds stood on the four trials became the assigned test score.

In addition to undertaking the SR test, a clinical type ataxia test on the occasion of undertaking the Test Battery our most recently tested subjects undertook two additional clinical type tests: (1) Stand One Leg Eyes Closed Test (SOLEC), and (2) Walk Line Eyes Closed Test (WALEC).

SOLEC

Subjects undertook this test upon completion of the Test Battery. The task as a static test consists of standing on each leg (SOLEC R and SOLEC L) with arms folded against chest and with eyes closed for a period of 30 seconds. Subjects were not permitted to make this a dynamic test by virtue of moving the standing foot in any way. Rather, it was required that the standing foot remain stationary. However, any amount of movement of the opposite leg or of the body was permitted so long as the body was maintained in an erect or near erect position. Subjects were permitted to close their eyes at any time after assuming a correct standing position. Subjects who violated the static foot requirement were stopped immediately and the number of seconds stood prior to violation constituted the trial score. Subjects began the test on the leg of their choice. Subjects who required more than one trial on each leg (for the perfect score criterion of 30 seconds) were requested to alternate legs on additional trials in the interest of reducing fatigue.

SOLEC performance was scored as follows: A perfect score on the first trial was weighted 5 and a score of 150 (30×5) was assigned; a perfect score on the second trial was weighted 4 and a score of 120 (30×4) plus the number of seconds stood on the first trial was assigned; a perfect score on the third trial was weighted 3 and a score of 90 (30×3) plus the number of seconds stood on the two previous trials was assigned; a perfect score on the fourth trial was weighted 2 and a score of 60 (30×2) plus the number of seconds stood on the three previous trials was assigned, with subjects requiring a fifth trial the total number of seconds stood on the five trials became the assigned test score.

WALEC[1]

Subjects undertook this test upon completion of the SOLEC. The test consists of walking as straight as possible a 12 foot long line on the floor at a typical (to the subject) speed with eyes closed, arms folded against chest, and feet heel to toe. Subjects alternated their starting positions from trial to trial. Each scorable trial required that subject walk the entire length of the line. The number of inches of deviation from the line at the end of its 12 foot length constituted a trial score, and the total of the *two best trials out of three* (best equaled least deviant from the line) constituted the test score.

[1] A major limitation of the WALEC procedure is that in notably ataxic individuals the qualitative performance is often more deviant than the individual's score would indicate. Accordingly, the WALEC would appear to be more of a test of spatial orientation than of ataxia or of postural equilibrium.

APPENDIX B. *Test Battery (Long Version) Raw Scores and Their Percentile Equivalents*

	Males									Females								
	Ages 13–16 (N = 42)			Ages 17–42 (N = 121)			Ages 43–50 (N = 9)			Ages 11–16 (N = 28)			Ages 17–42 (N = 112)			Ages 43–50 (N = 7)		
Percentile	W*	S/O*	S/C*	W	S/O	S/C	W	S/O	S/C	W	S/O	S/C	W	S/O	S/C	W	S/O	S/C
99th	60	553	330	60	610	420	60	566	367	60	552	312	60	605	430	60	515	373
98th	59	570	317	59	595	402	59	559	340	59	519	310	59	601	422	59	511	362
97th	59	545	315	59	585	385	59	553	314	59	517	337	58	580	415	59	513	354
96th	58	512	312	59	575	370	59	519	287	58	515	334	57	570	395	59	512	313
95th	58	539	339	59	565	315	59	514	261	57	510	325	57	560	385	58	511	331
90th	58	525	325	59	530	320	59	539	235	57	531	321	57	530	365	58	509	318
80th	56	510	285	58	519	295	59	509	230	55	521	284	55	520	300	52	508	306
70th	54	505	244	57	510	270	59	504	192	53	511	276	54	510	280	46	507	256
60th	53	495	220	57	501	240	58	503	177	52	507	244	52	500	270	45	498	234
50th	51	485	171	55	495	200	58	500	116	51	501	233	51	498	230	44	496	144
40th	50	460	150	54	480	165	56	499	79	49	501	205	50	485	210	43	442	112
30th	48	435	140	52	460	134	55	402	77	48	478	187	48	468	169	42	438	119
25th	47	425	125	51	415	115	52	396	75	47	461	179	47	460	145	41	437	92
20th	46	410	104	50	430	90	50	361	70	47	450	166	46	450	130	40	435	75
15th	45	401	84	49	403	79	49	312	56	47	441	157	46	430	115	39	434	60
10th	43	392	80	48	402	65	48	270	41	46	420	122	45	410	80	39	434	60
9th	42	385	75	47	395	62	48	270	41	46	415	121	45	405	78	39	434	60
8th	41	370	70	47	390	58	48	270	41	45	411	121	45	400	77	39	431	60
7th	40	359	65	46	385	55	48	270	41	45	407	120	44	395	76	39	431	60
6th	39	349	55	46	380	53	48	270	41	44	405	110	44	310	75	39	431	60
5th	38	330	51	46	375	51	48	270	41	43	403	100	42	368	70	39	431	60
4th	37	315	48	45	365	49	48	270	41	43	401	90	41	315	65	39	431	60
3rd	35	305	44	44	351	47	48	270	41	43	401	90	41	320	55	39	431	60
2nd	35	305	44	43	330	45	48	270	41	43	401	90	40	305	47	39	434	60
1st	35	305	44	42	291	45	48	270	41	43	401	90	38	299	33	39	434	60

* Walk H/T (six rails) * Stand F/O (six rails) * Stand F/C (six rails)

stood on the first two trials became the assigned test score, with subjects requiring a fourth trial the total number of seconds stood on the four trials became the assigned test score

In addition to undertaking the SR test, a clinical type ataxia test on the occasion of undertaking the Test Battery our most recently tested subjects undertook two additional clinical type tests (1) Stand One Leg Eyes Closed Test (SOLEC), and (2) Walk Line Eyes Closed Test (WALEC)

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SOLEC performance was scored as follows A perfect score on the first trial was weighted 5 and a score of 150 (30 × 5) was assigned, a perfect score on the second trial was weighted 4 and a score of 120 (30 × 4) plus the number of seconds stood on the first trial was assigned, a perfect score on the third trial was weighted 3, and a score of 90 (30 × 3) plus the number of seconds stood on the two previous trials was assigned a perfect score on the fourth trial was weighted 2 and a score of 60 (30 × 2) plus the number of seconds stood on the three previous trials was assigned with subjects requiring a fifth trial the total number of seconds stood on the five trials became the assigned test score

WALEC

Subjects undertook this test upon completion of the SOLEC The test consists of walking as straight as possible a 12 foot long line on the floor at a typical (to the subject) speed with eyes closed, arms folded against chest and feet heel to toe Subjects alternated their starting positions from trial to trial Each scorable trial required that subject walk the entire length of the line The number of inches of deviation from the line at the end of its 12 foot length constituted a trial score and the total of the *two best trials out of three* (best equaled least deviant from the line) constituted the test score

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THE INFLUENCE OF THE TONIC NECK REFLEX: VERTICAL WRITING

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From the Motor Learning Research Laboratory, Medical School and School of Education, and the Department of Physical Education for Women, University of Wisconsin

The influence of shoulder girdle position on the elaboration of the tonic neck reflex in man was investigated The subjects were twelve normal adult women volunteers They volitionally positioned the head to simulate the classical tonic neck reflex postures of Magnus and de Kleijn (1912) Fukuda's vertical writing test (1961) was administered as the diagnostic instrument A total of 1810 synchronous biplane photographs and 72 columns of letters or circles were interpreted Data analysis showed that shoulder girdle positioning blocked or enhanced the influence of the head positioning on the extremity used in vertical writing

Work done at the University of Illinois (Hellebrandt *et al*, 1956) demonstrated that severe exercise of muscle groups activating the wrist evoked total limb synergies and spontaneous positioning of the head in postures which then aroused facilitatory tonic neck reflexes Subsequent work in the Motor Learning Research Laboratory (Hellebrandt & Waterland, 1962, Waterland & Hellebrandt, 1964, Waterland & Munson, 1964 *a*) demonstrated that the overt pattern configurations were susceptible to (1) variations in the sensory input from radioulnar position and to volitional radioulnar joint movement, (2) variations in the way the assigned task was accomplished However, the relationship of the head to the shoulder girdle appeared to be constant This was confirmed by Waterland & Munson (1964 *b*) and it was then established *first, that stress per se* was not implicated in the head-shoulder girdle linkage, and *second*, that the *phenomenon* was indeed a two-way stereotype elicited by volitional

Supported in part by the Easter Seal Research Foundation National Society for Crippled Children and Adults the Research Committee of the Graduate School from funds supplied by the Wisconsin Alumni Research Foundation and from a General Research Support Grant to the University of Wisconsin Medical School from the National Institutes of Health Division of Research Facilities and Resources, Bethesda, Maryland

APPENDIX C *Test Battery (Short Version) Raw Scores and Their Percentile Equivalents*

	Males									Females								
	Ages 17–42 (N = 235)			Ages 43–50 (N = 360)			Ages 51–53 (N = 11)			Ages 18–29 (N = 41)			Ages 30–49 (N = 17)			Ages 50–59 (N = 11)		
Percentile	W[a]	S/O[b]	S/C[c]	W	S/O	S/C	W	S/O	S/C	W	S/O	S/C	W	S/O	S/C	W	S/O	S/C
99th	15	163	180	15	125	180	15	41	42	15	61	180	15	18	180	15	27	121
98th	15	116	179	15	66	177	15	39	41	15	58	175	15	44	174	15	25	118
97th	15	137	177	15	56	175	15	37	40	15	56	170	15	40	169	15	24	115
96th	15	128	176	15	46	172	15	35	39	15	54	165	14	36	163	15	23	111
95th	15	122	174	15	42	170	15	33	38	15	52	160	14	34	144	15	22	107
90th	15	71	173	14	30	136	14	32	35	15	50	153	13	32	120	14	19	103
80th	15	50	172	13	21	81	13	16	27	14	44	150	12	24	80	13	18	89
70th	14	39	154	12	20	54	12	14	23	13	32	107	11	20	60	10	17	58
60th	13	30	123	11	17	43	11	12	21	12	25	90	10	17	39	9	15	33
50th	13	25	92	10	15	33	10	11	20	11	21	64	10	16	31	8	13	30
40th	12	22	68	9	14	28	9	10	18	11	18	51	9	14	24	7	11	25
30th	11	19	47	8	12	23	7	9	16	10	16	33	8	12	20	6	9	19
25th	10	17	39	8	11	21	6	9	16	10	15	28	7	11	18	5	8	19
20th	10	16	35	7	10	19	4	8	15	9	14	26	7	10	15	4	7	18
15th	9	15	26	7	10	15	2	8	14	8	12	22	6	9	12	3	7	15
10th	8	13	20	6	9	11	1	7	13	7	12	18	6	8	11	3	7	12
9th	8	13	19	6	9	14	1	7	13	7	12	18	5	7	11	2	6	9
8th	8	13	18	6	8	13	1	7	12	6	12	18	5	7	11	2	6	6
7th	7	12	17	5	8	13	1	6	11	6	12	17	5	6	11	2	6	6
6th	7	11	16	5	8	12	1	6	11	6	12	17	5	6	10	2	6	6
5th	6	11	15	5	7	12	0	6	11	5	11	16	4	6	10	2	5	6
4th	5	10	15	5	7	11	0	6	11	5	11	15	4	6	10	1	5	5
3rd	5	9	14	5	7	10	0	5	11	5	11	14	4	5	9	1	5	5
2nd	4	9	13	4	6	9	0	5	11	4	10	13	3	5	8	1	5	5
1st	4	8	12	3	5	8	0	5	11	3	9	8	2	5	6	1	5	5

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Percentile	Males									Females								
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	W[a]	S/O[b]	S/C[c]	W	S/O	S/C	W	S/O	S/C	W	S/O	S/C	W	S/O	S/C	W	S/O	S/C
99th	15	163	180	15	125	180	15	41	42	15	61	180	15	48	180	15	27	121
98th	15	146	179	15	66	177	15	39	41	15	58	175	15	44	171	15	25	118
97th	15	137	177	15	56	175	15	37	40	15	56	170	15	40	169	15	24	115
96th	15	128	176	15	46	172	15	35	39	15	54	165	14	36	163	15	23	111
95th	15	122	174	15	42	170	15	33	38	15	52	160	14	31	141	15	22	107
90th	15	74	173	14	30	136	14	32	35	15	50	153	13	32	120	14	19	103
80th	15	50	172	13	24	81	13	16	27	14	44	150	12	24	80	13	18	89
70th	14	39	154	12	20	54	12	14	23	13	32	107	11	20	60	10	17	58
60th	13	30	123	11	17	43	11	12	21	12	25	90	10	17	39	9	15	33
50th	13	25	92	10	15	33	10	11	20	11	21	64	10	16	31	8	13	30
40th	12	22	68	9	14	28	9	10	18	11	18	51	9	14	24	7	11	25
30th	11	19	47	8	12	23	7	9	16	10	16	33	8	12	20	6	9	19
25th	10	17	39	8	11	21	6	9	16	10	15	28	7	11	18	5	8	19
20th	10	16	35	7	10	19	4	8	15	9	11	26	7	10	15	4	7	18
15th	9	15	26	7	10	15	2	8	14	8	12	22	6	9	12	3	7	15
10th	8	13	20	6	9	14	1	7	13	7	12	18	6	8	11	3	7	12
9th	8	13	19	6	9	14	1	7	13	7	12	18	5	7	11	2	6	9
8th	8	13	18	6	8	13	1	7	12	6	12	18	5	7	11	2	6	6
7th	7	12	17	5	8	13	1	6	11	6	12	17	5	6	11	2	6	6
6th	7	11	16	5	8	12	1	6	11	6	12	17	5	6	10	2	6	6
5th	6	11	15	5	7	12	0	6	11	5	11	16	4	6	10	2	5	6
4th	5	10	15	5	7	11	0	6	11	5	11	15	4	6	10	1	5	5
3rd	5	9	14	5	7	10	0	5	11	5	11	14	4	5	9	1	5	5
2nd	4	9	13	4	6	9	0	5	11	4	10	13	3	5	8	1	5	5
1st	4	8	12	3	5	8	0	5	11	3	9	8	2	5	6	1	5	5

THE INFLUENCE OF THE TONIC NECK REFLEX VERTICAL WRITING

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The influence of shoulder girdle position on the elaboration of the tonic neck reflex in man was investigated The subjects were twelve normal adult women volunteers They volitionally positioned the head to simulate the classical tonic neck reflex postures of Magnus and de Kleijn (1912) Fukuda s vertical writing test (1961) was administered as the diagnostic instrument A total of 1810 synchronous biplane photographs and 72 columns of letters or circles were interpreted Data analysis showed that shoulder girdle positioning blocked or enhanced the influence of the head positioning on the extremity used in vertical writing

Work done at the University of Illinois (Hellebrandt *et al* 1956) demonstrated that severe exercise of muscle groups activating the wrist evoked total limb synergies and spontaneous positioning of the head in postures which then aroused facilitatory tonic neck reflexes Subsequent work in the Motor Learning Research Laboratory (Hellebrandt & Waterland 1962 Waterland & Hellebrandt 1964 Waterland & Munson 1964 *a*) demonstrated that the overt pattern configurations were susceptible to (1) variations in the sensory input from radioulnar position and to volitional radioulnar joint movement (2) variations in the way the assigned task was accomplished However the relationship of the head to the shoulder girdle appeared to be constant This was confirmed by Waterland & Munson (1964 *b*) and it was then established *first* that stress *per se* was not implicated in the head shoulder girdle linkage and *second* that the phenomenon was indeed a two way stereotype elicited by volitional

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movement of the head or of the upper extremities The purpose of this *investigation was to show that shoulder girdle fixation is capable of suppressing the normal evolution of the tonic neck reflex*

METHOD

The subjects of the investigation were twelve normal adult women volunteers, one of whom was left handed All were in the undergraduate program of the Physical Education and Occupational Therapy Departments at the University of Wisconsin None of the students had previous experience as subjects or assistants in the laboratory. All were uninformed as to the objective of the study

The vertical writing test devised by Fukuda (1959) was administered as the diagnostic instrument He used the procedure originally to establish the *imbalance of muscle tone resulting from labyrinthine influence normally* present in humans In 1961 Fukuda used the same test to show objectively that the tonic neck reflex in healthy adults "regulates, though latently, relative movements of the head and upper extremity". He concluded that change in muscle tonus existed as a result of head positioning and was revealed in the dominant extremity as a deviation in the outcome of the willed act

For these experiments a comfortable sitting position was assumed by the subject at a table of suitable height Paper measuring 71 cm × 43 cm was used during the lettering of the word "Japan" or the drawing of circles in vertical columns The pencil, held in the subject's dominant hand, was positioned at the midline of the body by placing its tip 2 5 cm from the top of the paper During the writing no part of the subject's body touched the table Between each test the paper was moved across the table an appropriate distance which required repositioning of the pencil by one of the investigators Two series of four trials were done with the head in a normal position first, with the subject looking directly ahead, second, a like position *but with the subject blindfolded On command the subject* volitionally positioned the head to simulate the classical sagittal plane (ventroflexion and dorsiflexion) and rotary movements (left and right) of Magnus & de Kleijn (1912) Three columns of letters were printed with the head in each position since the effect of the head posture is stated to be latent (Fukuda, 1961) Each change in head orientation was preceded by a normal position (eyes covered) to allow time for the influence to dissipate

In addition to the vertical writing test used by Fukuda (1959) biplane photographs were taken every two seconds to record and identify the autonomous components of the willed movement Robot and Praktina 35 mm cameras were placed so that serial side (dominant) and frontview pictures could be taken of the subject The cameras were synchronized by a Simenco control box The photographic results, brought to a 3 5 × 5 inch

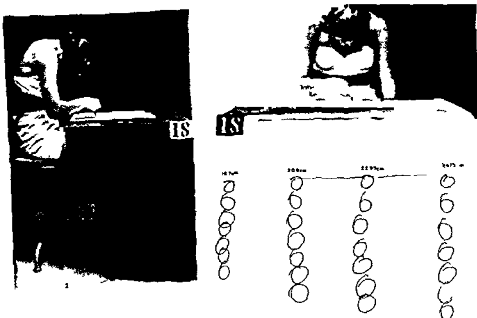


Fig. 1. Biplane photograph of patterning resulting from voluntary ventroflexion of the head. Initial column of circles drawn with the head in a normal position. The last three columns reflect the influence of the head-shoulder relationship. Centimeter measures above each column designate the length before being reduced in size.

size by using a Valoy II enlarger and a Kriser Roller Printer, were subjected to inspectional analysis.

The vertical column of letters or circles were quantified. A line was drawn from the center of the first letter or circle to the center of the last. The angle of deviation (left minus or right plus) was then measured in degrees with a protractor from a line perpendicular to the starting mark. The length of the columns was measured in centimeters along the same perpendicular from the top of the first letter or circle to the bottom of the last.

RESULTS AND THEIR INTERPRETATION

The results were based on 12 experimental sessions, one for each subject. A total of 1810 synchronous biplane photographs and 72 columns of letters or circles were interpreted.

Analysis of the photographic records and the vertical writing test showed that whenever the shoulder girdle was fixed in a way antagonistic to

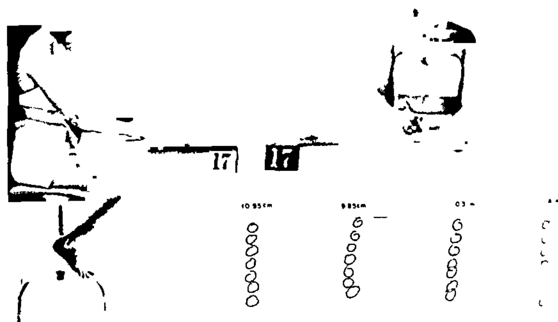


FIG 2 Biplane photograph of the motor configuration when the shoulder girdle was maintained in a fixed position during ventroflexion of the head The vertical columns of circles reflect the influence of the stabilized shoulder position

the normal development of the reflex, changes in head positioning did not have the anticipated influence on the distribution of the tonus in the dominant extremity In contrast, when the shoulder girdle was positioned to enhance the motor act the subjects demonstrated the expected deviations in the verticality or lengthening of the column of letters

Behavioral Response to Ventroflexion and Dorsiflexion of the Head

Volitional ventroflexion of the head enhanced the starting position of shoulder girdle protraction and caused spinal flexion in nine of the twelve subjects Figure 1 shows a typical overt configuration and the expected lengthening of the column of circles The mean length of the vertical column of letters or circles for these subjects was 7 64 cm as compared with a mean of 6 68 cm for the normal head position Fukuda (1961) attributed the increase in column length to a decrease in muscle tonus of the extremity, however, the "key" seems to lie in the involvement of the proximal muscles and hence the overt shoulder girdle positioning

Figure 2 demonstrates the posture assumed by the remainder of the subjects, the head was brought forward into ventroflexion but the shoulders were retracted and the spine stabilized The resulting vertical columns of letters showed a decrease in mean length rather than the expected in-

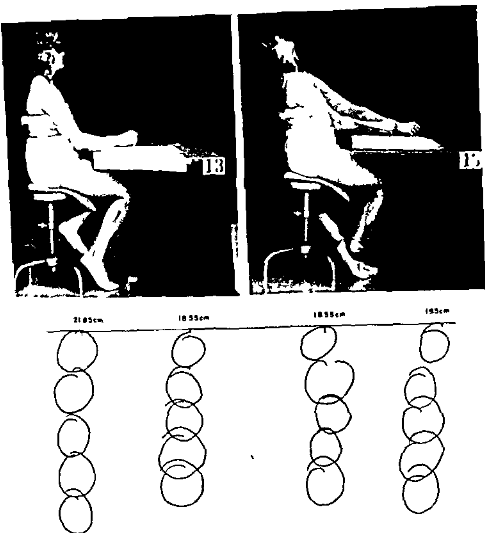


FIG 3 Left photograph depicts subject drawing the first column of circles, head in normal position Right picture illustrates subject's starting position with head in dorsiflexion and a superimposed image taken close to the end of the same column Shortening of the columns resulted from shoulder retraction even though simultaneous hip extension minimized the difference in the length of the columns for the dorsiflexed head position

crease the mean for the three subjects normal head positions, with a blindfold, was 7 54 cm and for head ventroflexion, 6 57 cm

Autonomous shoulder retraction and spinal extension were movement concomitants for five subjects during voluntary dorsiflexion of the head and yielded a mean column length of 6 73 cm as compared with 7 18 cm for the column of circles with the head in a normal position Shortening of the columns of circles and the overt patterning is illustrated in Fig 3

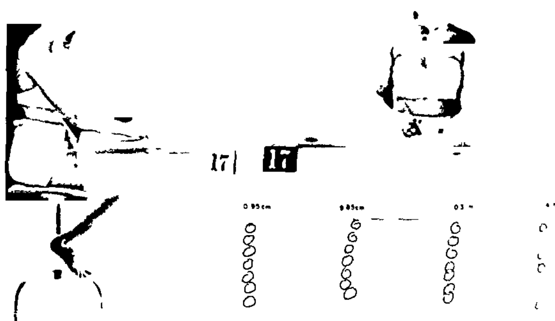


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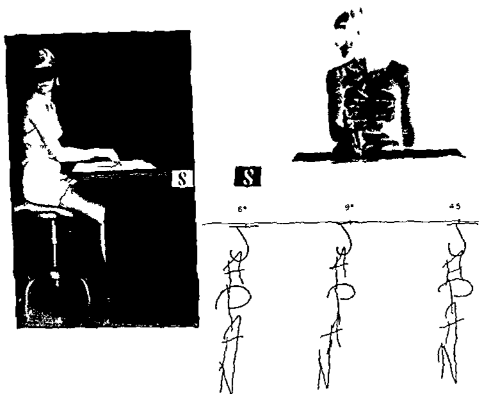


Fig 5 Biplane photograph of the same subject pictured in Fig 4 with the head rotated to the right Column deviation to the left resulted from shoulder protraction in the starting position The deviation in verticality of the word Japan' resembles that for head rotation left

Behavioral Response to Rotation of the Head to the Left and Right

The numerical data resulting from rotation of the head to the left resulted in a mean of minus 2.63 degrees of deviation from the midline Twenty one of the subjects thirty six vertical columns deviated toward the non dominant side Protraction of the ipsilateral or skull shoulder was observed in the photographs as illustrated in Fig 4 Positioning of the pencil brought the shoulder into protraction and the subjects were unable to yield to shoulder retraction when the head was rotated to the right The results were approximately the same for both rotation test situations (Fig 5)

Fukuda (1961) found that rotation of the head to the left caused a deviation of the column to the right A slant in verticality of the column to the left was apparent for rotation of the head to the right However, he stated that this phenomenon is not so high as in the case of writing with the head prone or supine, but it still has been as high as 50 60% His percentages based on an unstated number of subjects, do

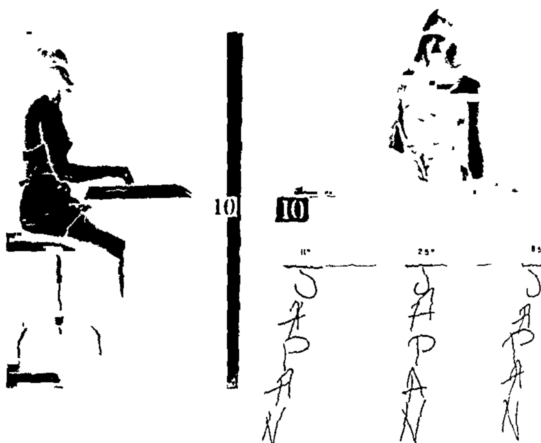


FIG 4 Biplane photograph of overt patterning resulting from volitional head rotation to the left The head position facilitated the starting posture imposed on the subject The amount of deviation to the left is expressed in minus degrees above each column

It seems reasonable to assume that the "key cue" to the extensor patterning and therefore a decrease in column length is caused by shoulder girdle retraction rather than a direct increase in muscle tonus of the "indicator limb" as suggested by Fukuda (1961)

Hip joint extension occurred in some subjects as the columns were being written, this joint action minimized the numerical results Stabilization of the shoulder girdle in the starting position by three subjects produced results much like the normal, both numerically and pictorially

An increase or a decrease in the length of vertical columns of letters or circles resulting from ventroflexion and dorsiflexion of the head respectively supports the findings of Fukuda (1961) The evidence herein reported strongly suggests that shoulder girdle protraction and spinal flexion are linked with volitional ventroflexion of the head Retraction of the shoulder girdle and spinal extension were movement concomitants of voluntary head dorsiflexion The above configurations may be the key components which caused the tonus changes in the "indicator limb" musculature as reported by Fukuda (1961)

provide insight into total movement synergies Once understood these may be used to facilitate motor learning and expedite the muscle re education of the disabled

SUMMARY AND CONCLUSIONS

The influence of shoulder girdle fixation on the elaboration of the tonic neck reflex in man was investigated Twelve normal subjects com pleted a like number of experimental sessions in which overt patterning resulting from voluntary head positioning and its influence on vertical writing was analyzed photographically and numerically A total of 1810 synchronous biplane photographs and 72 columns of letters or circles were interpreted The evidence supports the following conclusions

1 The influence of the tonic neck reflex is blocked or enhanced by shoulder girdle positioning

2 Bilateral protraction of the shoulders and spinal flexion were augmented by voluntary ventroflexion of the head The effect of the head positioning was reflected by a lengthening of the vertical column of letters

3 Retraction of the shoulders and spinal extension were movement con comitants of voluntary dorsiflexion of the head The resulting effect was a shortening of the column of vertical letters

4 Protraction of the shoulder on the skull side was facilitated by voluntary rotation of the head to the left and resulted in a deviation of the vertical column of letters to the left

5 Volitional head rotation to the right should have resulted in retraction of the shoulder on the jaw side but was blocked by the starting position The slight deviation of the column of letters to the left was in keeping with the shoulder girdle positioning

ACKNOWLEDGMENT

The interest and advice given by Dr F A Hellebrandt is gratefully acknowl edged

RESUME

On a examiné l'influence de la position de la ceinture d'épaules sur l'élargisse ment du réflexe tonique du cou dans l'homme Les sujets étaient douze femmes adultes normales qui se sont prêtées à cette expérience Elles ont volontairement placé la tête de manière à simuler les postures classiques toniques réflexes du cou de Magnus et de de Kleijn (1912) Le test de l'écriture verticale de Fukuda a été administré comme instrument diagnostique On a interprété 1810 photo graphies biplanes synchroniques et 72 colonnes de caratères au courbes (*circles*) L'analyse des données a démontré que la position de la ceinture d'épaules a entravé ou accentué l'influence de la position de la tête sur le bras (*extremity*) dont on s'est servi pour écrire verticalement

not negate the evidence presented which suggests that the shoulder girdle is of importance and that the column will slant in a direction that is in keeping with its positioning

DISCUSSION

The shoulder girdle musculature seems capable of facilitating or inhibiting the outflow from the tonic neck reflex to the distal segments Ventroflexion and rotation of the head to the non-dominant side utilized and augmented the starting position for vertical writing The numerical results and overt configurations viewed from the photographs for the two tests were highly consistent within and between subjects In a previous study conducted in the Motor Learning Research Laboratory ventroflexion of the head was linked with protraction of the shoulder girdle, spinal flexion, medial rotation and abduction of the arm at the glenohumeral joint (Waterland & Hellebrandt, 1964) Rotation of the head caused a similar unilateral response in the shoulder and limb on the skull side These components originally identified under stress were incorporated into what was called a flexor motor figure It was also found that the ergographic exercise of volitional radioulnar pronation, a forearm position assumed in writing, belonged to this flexor configuration (Waterland & Munson, 1964 *a*) Vertical writing with the head in a position of ventroflexion or rotation to the non-dominant side evoked this integrated flexor patterning The flexor motor figure resulted in an elongation of the vertical column of letters Head rotation to the non-dominant side caused a slant in column verticality to the same side

Dorsiflexion of the head and rotation toward the dominant side in the vertical writing test should have augmented an extensor motor figure (Waterland & Hellebrandt, 1964) Shoulder girdle retraction, spinal extension, upper limb lateral rotation and adduction were evident in the configuration if the patterning was not blocked by shoulder girdle stabilization in the starting position Volitional head rotation to the dominant side coupled with retraction of the shoulder girdle, lateral rotation and adduction of the upper limb should have resulted in a deviation of the letters to the dominant side rather than to the opposite side as reported by Fukuda (1961) Since the shoulder girdle was fixed in the protracted starting position, the results from the dorsiflexed head posture were more in keeping with those recorded for ventroflexion and rotation of the head to the non-dominant side

The important point in the current study is that the normal elaboration of the tonic neck reflex is blocked or enhanced by shoulder girdle positioning This is strong presumptive evidence in support of our hypothesis that the tonic neck reflex is, in some way as yet undefined, mediated through the functional elements which link axial and appendicular musculature Studies of this type lead to the identification of key cues which

INFLUENCE OF SIDE POSITION OF THE HEAD ON CENTRAL AND FLASH NYSTAGMUS IN THE RABBIT

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The influence of side position was studied for two forms of optic nystagmus flash nystagmus, following exposure of one eye to intermittent photic stimulation, and central nystagmus evoked by electrical stimulation of a single optic pathway Flash nystagmus to the right, elicited from the right eye, is enhanced by right and depressed by left side position Central nystagmus shows the same behavior, if the eyes are kept in the dark If they are exposed to light, the dual influence of labyrinthine impulses on central nystagmus may be obscured by changes in photic inhibition, due to varying conditions of illumination of the two eyes in side position

In the rabbit, it is possible to evoke "optic nystagmus" by various forms of stimulation of an optic pathway (1) By flashing of a single eye ("flash nystagmus" Costin, Chaimovitz & Bergmann, 1965), (2) by electrical excitation of a single optic pathway, from retina to superior colliculus ("central nystagmus", Gutman *et al*, 1963 *b*, Bergmann *et al*, 1964), and (3) by optokinetic stimulation All forms of optic nystagmus are subcortical phenomena, i e they are independent of the presence of the optic cortex (Bergmann et al 1964, Scala & Spiegel, 1941)

The neurons of the various optic relay stations must establish close contact with those of the vestibular pathway, as both systems are involved in the regulation of nystagmus Interaction of the optic and the labyrinthine mechanisms can be demonstrated in various ways Thus, central nystagmus can be enhanced or suppressed by angular acceleration or deceleration of the animal, depending on the direction of the separate responses (Lachmann *et al* 1958) The most striking demonstration of the relationship between the visual system and the vestibular apparatus is, however, obtained by a form of optic stimulation, such as permanent illumination from a stationary light source or high-frequency flashing which by itself does not evoke eye movements, but has a pronounced inhibitory effect on labyrinthine nystagmus. We have shown recently that in the rabbit photic inhibition has an asymmetric character, i e illumination of one eye suppressed only the eye movements induced by stimulation of the contra-

ZUSAMMENFASSUNG

Es wurde untersucht welchen Einfluß die Lage des Schultergurtels auf den tonischen Halsreflex beim Menschen hat Die Versuchspersonen waren zwolf normal entwickelte weibliche Freiwillige Sie brachten den Kopf bewußt in eine Lage welche die klassischen tonischen Halsreflexhaltungen von Magnus und de Kleijn (1912) simulierte Um zu einer Diagnose zu kommen wurde Fukudas vertikaler Schreibtest (1961) angewandt Es wurden insgesamt 1810 synchrone Photographien in zwei Ebenen und 72 Reihen von Buchstaben oder Kreisen ausgewertet Die Analyse der Ergebnisse ergab daß die Schultergurtelhaltung den Einfluß der Kopfhaltung auf die beim vertikalen Schreiben gebrauchten Extremitaten blockierte oder verstarkte

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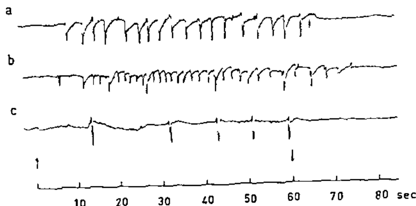


Fig 1 Influence of side position on flash nystagmus Right eye flashed at 30/sec for 60 sec (as indicated by arrows) Left eye covered with a small black hood (a) Rabbit in prone position 17 eye beats to right, followed by 2 afterbeats (b) Animal placed on right side 28 eye movements and 4 afterbeats (c) Left side position Only 5 movements

turned very slowly by 90° and the animal kept in the new condition for at least 2 min before stimulation was started

RESULTS

Of the 3 forms of optic nystagmus described above, only central and flash nystagmus were used because here excitation of one optic pathway always leads to eye movements in a single direction On the other hand the response to monocular optokinetic stimulation depends on the direction in which the object moves through the visual field and is altered by tilting of the head, because the position of the image relative to the receptive fields of the retina is changed

A Dual Influence of Side Position on Flash Nystagmus

In Fig 1 we show as an example nystagmus to the right, evoked by flashing of the right eye under 3 different conditions when the animal is kept in prone position (Fig 1 *a*) when it is turned to the right side, where marked enhancement is apparent (Fig 1 *b*) and in left side position where the response is strongly depressed (Fig 1 *c*) A number of such experiments are summarised in Table 1 In several cases, combination of monocular flashing with ipsilateral side position could elicit a response in animals which were refractory in prone position (see example 5 in the Table)

Attention should be drawn to the fact that the two eyes of a rabbit do not react equally to intermittent photic simulation and do not show the same degree of reinforcement or inhibition when the head is tilted The reasons for the large differences in susceptibility to flashing will be discussed in a future paper

lateral labyrinth (Bergmann *et al.*, 1965). This asymmetry was related to the fact that in the rabbit's chiasm the optic fibers, emanating from the two retinas, undergo an almost complete decussation and thus remain separated throughout (Polyak, 1957).

The intimate connection between optic and labyrinthine pathways makes it probable that vestibular impulses will also influence optic nystagmus. Such a relationship may be uncovered most easily if a form of labyrinthine stimulation is selected that by itself does not evoke nystagmus, in analogy to the principle by which photic inhibition of vestibular nystagmus was demonstrated (Bergmann *et al.*, 1965). In the intact awake animal, side position never leads to eye movements, although the two labyrinths undergo unequal stimulation (Nylen, 1950). In a previous study on central nystagmus (Gutman, Chaimovitz & Bergmann, 1963 *a*), it was reported that by turning the head to either side, the response is enhanced, albeit to a different degree for left and right side position. We shall show here that side position has a marked asymmetric effect on optic nystagmus, i.e. tilting the head to one side enhances the response, while the opposite position produces inhibition. The reasons for the divergent results reported previously will be discussed.

METHODS

Forty rabbits of either sex, weighing between 1.5 and 3.5 kg were used. During the tests they were kept in a hammock which permitted free movement of head and legs.

For intermittent photic stimulation, a Strobotest No. II photostimulator was placed at a distance of 50 cm from the center of the cornea, while the second eye was covered with a small black hood.

For central nystagmus, bipolar, concentric electrodes were introduced under ether anesthesia into the optic nerve, the optic tract, the superior colliculus or the diencephalic nystagmogenic area (Bergmann *et al.*, 1959). At the end of this procedure, the wounds were infiltrated with 2 per cent xylocaine; the experiment began only after recovery from general anesthesia. The electrode positions were checked in each experiment by histological control.

Square wave pulses of 2 msec duration were supplied from a Tektronix pulse generator and were continuously monitored on a Tektronix type 502 oscilloscope. The pulse generator triggered a constant current source, constructed by Mr. J. Weinman of the Rogoff Laboratory of Medical Electronics of this Medical School, and supplying currents between 1 μA and 10 mA. The currents actually used were in the range of 0.1–0.5 mA.

Nystagmograms were recorded on a Schwarzer electroencephalograph by means of 2 needle-like electrodes. These were implanted underneath the skin, near the angles of one palpebral commissure, using local anesthesia with 2 per cent xylocaine.

In order to test nystagmus responses in side position, the hammock was

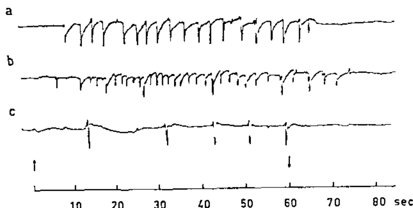


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TABLE 1. *Influence of side position on flash nystagmus*

One eye was stimulated with 30 f/sec, which *had been determined previously as the* optimal rate (Costin *et al* 1965), flash intensity 10^5 lux The second eye was covered with a small black hood

Example No	Flashing of right eye			Flashing of left eye		
	Prone	Right side	Left side	Prone	Right side	Left side
1	17	32+2[a]	5	21	3	40
2	24	43	5	32	9	50
3	8	26	3	11	5	22
4	26+1	95+9	4	43	13	153+12
5	0	2	0	0	0	7

[a] These figures read as follows 32 eye movements during flashing and 2 afterbeats

B *Effect of Side Position on Central Nystagmus*

The results in paragraph A are in disagreement with our earlier report on central nystagmus (Gutman, Chaimovitz & Bergmann, 1963 *a*) It was then shown that e g central nystagmus to the left is enhanced by either side position, but more so by tilting the head to the left than to the right side These results contradict the above observations on flash nystagmus, although both responses use the same central mechanism, viz excitation of the optic pathway

Closer inspection of the experimental conditions employed previously and in the present series revealed only one difference, viz during flashing the non-exposed eye was always kept protected from light, whereas in the earlier experiments on central nystagmus both eyes were open At that time, the asymmetric character of photic inhibition was not yet recognised

Direct measurement with a luxmeter shows that the amount of diffuse light falling on the eye varies with head position Thus, under the conditions of the present experiments, the intensity of light near the cornea was *about* 1000 lux, whether the eye was directed to the ceiling or to the walls of the room, but was reduced to $^1/_{10}$, when the eye was looking to the floor, and even to $^1/_{100}$ when the light reaching the cornea was reflected from the working table As will be demonstrated, these variations in intensity of illumination may simulate enhancement in situations in which inhibition is expected

In Fig 2 we first show central nystagmus when both eyes of the rabbit were protected from light In prone position, stimulation of the right optic tract evoked nystagmus to left (Fig 2 *a*) Placing the head on its left side enhanced the reactions strongly (Fig 2 *b*), while tilting the animal to the right side caused marked inhibition (Fig 2 c) When the same series of tests was repeated while both eyes were open, the animal did not respond

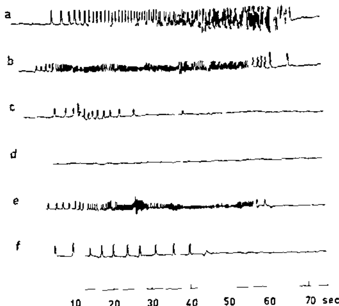


FIG 2 Influence of side position on central nystagmus Concentric electrodes in right optic tract *stimulation at 40 c s pulse duration 2 msec* current strength 0 2 mA nystagmus to left (upward excursion) Stimulation period of 60 sec indicated by arrows Only in *b* stimulation extended over 55 sec because of a technical error (*a c*) Both eyes covered with black hoods (*a*) Rabbit in prone position Latency of 8 sec 98 eye beats afternystagmus 12 movements (8 sec) (*b*) Head placed on left side (left ear pointing to the ground) Latency of 3 sec 138 eye beats (during 55 sec) 9 afterbeats (*c*) Head on right side Response dies out after 27 sec (12 beats) 2 additional beats had only a very small *amplitude (d f) Both eyes open Intensity of* light in operation room 1000 lux (*d*) Prone position No response (*e*) Head on left side 104 eye beats to left (*f*) Head on right side after 41 sec (10 beats) the nystagmus dies out

at all in prone position due to the inhibitory effect of light (Bergmann *et al* 1965) (Fig 2 *d*) In left side position a strong response appeared (Fig 2 *e*) However even when the head was turned to the right side a response was elicited although it was much weaker (Fig 2 *f*) The right i e the inhibitory eye, receives nearly the same amount of radiation in Fig 2 *d* and *e* Therefore the degree of photic inhibition is equal, and the difference in the nystagmus responses *truly expresses the synergistic effect* of labyrinthine stimulation On the other hand in Fig 2 *f* illumination of the right eye is diminished thus reducing photic inhibition strongly This effect overshadows the inhibition that results from labyrinthine impulses Therefore the overall reaction in Fig 2 *f* is stronger than the response in prone position (Fig 2 *d*)

Table 2 represents a number of similar experiments in which the eyes of the rabbits were either covered or exposed to light The influence of side position is independent of the actual localisation of the electrodes and is determined solely by the *direction of the eye beats*

TABLE 2 *Dual effect of side position on central nystagmus*

All stimulations at 40 c/sec 2 msec duration for a period of 60 sec but intensities varying from case to case Note that stimulation of the optic nerve evokes ipsiversive nystagmus while excitation of optic tract superior colliculus or nystagmogenic area causes contraversive eye movements

Example No	Electrodes at	Direction of eye beats to	Position of head		
			Prone	Right side	Left side
A *Both eyes covered*					
1	left optic nerve	left	70 + 2[a]	39	125 + 2
	right optic nerve	right	24	52	[illegible]
2	left optic nerve	left	90 + 11	96	185 + 25
	right optic nerve	right	70 + 5	140 + 15	2
3	left optic tract	right	6	20	2
4	right optic tract	left	85	25	125
5	left superior coll	right	5	39	1
	right superior coll	left	10	4	40
6	left superior coll	right	9	53	1
	right superior coll	left	42	17	60
7	left nystagm area	right	47	67	23
	right nystagm area	left	100 + 14	21	150 + [illegible]
8	right nystagm area	left	72 + 5	27	114 + 6
B *Both eyes open*					
9	left nystagm area	right	48 + 3	125 + 15	69 + 4
	right nystagm area	left	80 + 4	110 + [illegible]	250 + 7
10	left nystagm area	right	0	14	7
	right nystagm area	left	39	115 + 15	140 + 20

[a] These figures read as follows 70 eye beats during electrical stimulation 2 after movements

DISCUSSION

In the schematic Figure 3 the anatomical arrangement of the hair cells in the maculae is shown In a given side position the hair cells of one saccule are exposed to pulling by the statolithic membrane and the cells of the other to pressure On the other hand, there is not much difference in the forces acting on the hair cells of the left and right utricles because the latter are arranged approximately in parallel

Since pulling is much more effective than pressure (Fischer & Wolfson, 1943) left side position will cause stronger stimulation of the left than of the right labyrinth Therefore in this situation the left labyrinth commands the over all effect although both labyrinths contribute to the reaction The present experiments establish the rule that stimulation of the left saccule by pulling forces enhances nystagmus to left and inhibits the eye beats to right Thus there exists a non symmetrical relationship between one labyrinth and the two optic pathways The above rule indicates that the fibers

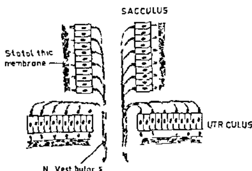


Fig. 3. Schematic representation of left and right maculae. The utricles are placed at an angle of 90° relative to the saccules, although in the rabbit's labyrinth the angle is slightly larger. Note that the utricular hair cells of both sides are arranged in parallell, while the saccular cells are pointing in opposite directions.

from each labyrinth reaching ultimately the oculomotor nuclei of both sides form excitatory synapses in one hemisphere and inhibitory ones with the corresponding neurons on the other side.

The present experiments do not reveal in which way optic nystagmus is influenced by the second labyrinth, where the saccule is stimulated by pressing the statolithic membrane against the hair cells. In the intact animal this effect—if present—is obscured by the overwhelming influence of simultaneous pulling on the contralateral hair cells. Information on this problem may be expected from experiments with unilaterally labyrinth-ectomised animals.

The relationship between retina and labyrinth is, however, not simply reciprocal. It has been pointed out previously (Bergmann *et al.*, 1965) that permanent illumination of the "non inhibitory" eye has no influence whatsoever on labyrinthine nystagmus, while in a given side position the same labyrinth inhibits contraversive optic nystagmus, but enhances the ipsiversive response. This divergence may be related to the different neural mechanisms involved. Stimulation of one retina by constant light or by high frequency flashing leads to suppression of the potentials along the optic pathway (Arden & Liu, 1960), suggesting that the resting activity of *the latter is necessary for the* nystagmus response. *On the other hand, the* impulses emitted from a given labyrinth are augmented by ipsilateral tilting of the head (Adrian, 1943). Optic inhibition is thus based on a "negative" mechanism while labyrinthine inhibition is the consequence of positive activation.

The effect of side position on optic nystagmus has been ascribed here mainly to stimulation of the saccular maculae. The question arises whether stimulation of the utricle is also capable of modifying optic nystagmus. Experiments in this direction will be reported elsewhere.

Previous studies on the influence of side position on central nystagmus indicated enhancement whether the head was tilted to left or right (Gut-

man, Chaimovitz & Bergmann, 1963 a) The present experiments show that this is due to a change in photic inhibition when the tests are carried out with both eyes open The amount of diffuse light reflected from the operation table is considerably smaller than the radiation emitted from walls or ceiling Comparison of the earlier observations with the present results reveals the importance of photic inhibition of nystagmus as compared to labyrinthine inhibition emanating from the statolithic organs

ACKNOWLEDGMENT

The authors wish to thank Mr B Knafo for preparation of the drawings

ZUSAMMENFASSUNG

Wir haben beim Kaninchen den Einfluss der Seitenlage des Kopfes auf zwei Formen von optischem Nystagmus geprüft nämlich auf den Blitznystagmus bei welchem ein Auge intermittierender photischer Reizung ausgesetzt ist und auf den zentralen Nystagmus hervorgerufen durch elektrische Stimulierung einer Sehbahn Blitznystagmus nach rechts wurde durch Reizung des rechten Sehnerven ausgelöst Die rechte Seitenlage verstärkt und die linke schwächt diese Reaktion Das gleiche Verhalten wird beim zentralen Nystagmus konstatiert falls die Augen zugedeckt sind Sind sie jedoch der Beleuchtung durch eine konstante Lichtquelle ausgesetzt so kann die photische Hemmung den doppelten Einfluss *vestibulärer Impulse auf den zentralen Nystagmus überlagern*

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VULNERABILITY OF THE ORGAN OF CORTI IN POISONING

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The direct effects of some toxic drugs (kanamycin, dihydrostreptomycin, chloramphenicol and quinine) upon the organ of Corti have been observed in the guinea pigs. The drug was injected into the middle ear cavity and subsequently reached the organ of Corti through the round window membrane. After several days the inner ear was taken out and stained with the reagents for succinic dehydrogenase or DPN diaphorase which were introduced into the tympanic scala through the round window. The following results were obtained.

1. Loss of the enzymes was more apparent in the cells with higher metabolic activities, such as the outer hair cells or the nerve endings.

2. Patterns of damage to the organ of Corti seemed to be almost identical. But a smaller difference between antibiotic poisoning and quinine poisoning was found.

Generally, it seemed to be possible that higher metabolic activities of the outer hair cells are responsible for weakness of the cells in pathologic processes in the ear.

INTRODUCTION

Numerous clinical and physiological investigations are available which aim at throwing light on the toxic action of drugs (e.g. streptomycin, dihydrostreptomycin, kanamycin, neomycin and quinine) on the ear. Patterson & Gulick (1963, 1964) have also indicated that chloramphenicol has a deleterious effect upon the cochlear response of an animal.

The pathological findings in the mammal ear after prolonged use of the drugs have been reported to be almost identical. The most striking pathological finding in the ear was damage to the hair cells of the organ of Corti. Most reports have shown that damage was severe in the outer hair cells but less severe in the inner hair cells. However, no definite conclusion concerning vulnerability of the hair cells to the drug has been found in the literature.

Hawkins (1959) has carried out a histological examination of the inner ear of animals treated with kanamycin. In one of the cats he has found that the inner hair cell nuclei were absent in all turns, while near the apex the outer hair cell nuclei were visible and hairs could be seen extending into the tectorial membrane. Further, according to Hawkins, Rahway &

Lurie (1952), in some of the inner ears of cats treated with streptomycin the inner hair cells were degenerated and the outer hair cells were present

Benitz, Schuknecht & Brandenburg (1962) have acquired the temporal bones from two patients suffering hearing loss from the administration of kanamycin and presented the graphic summarization of the histopathological findings of the ears In most areas of the inner ear in both cases histological changes have been severe in the outer hair cells but less severe in the inner hair cells However in some areas of the inner ear the inner hair cells have appeared normal although the outer hair cells have been damaged

Covell (1936) and Ruedi *et al* (1952) have reported that the degenerative changes due to systemic administration of quinine began in the outer hair cells But Hinohara (1961) has often observed that histological changes caused by administration of this drug have been severe in the inner hair cells but less severe in the outer hair cells His observation on toxic effects of kanamycin and dihydrostreptomycin on the inner ear of guinea pig has resulted in similar findings

In addition Lindsay Proctor & Work (1960) have presented the histologic findings in a human which followed neomycin therapy In reviewing this case the toxic effect of the drug on the inner ear has been evident mainly by degeneration of the inner hair cells and to a lesser extent the outer hair cells

An important problem should be presented if we intend to clarify vulnerability of the hair cells We think it is the problem concerning the pathway of the drug into the inner ear from the blood vessels Ruedi (1951) believed that the drug (streptomycin or quinine) taken into the inner ear by the blood stream passes the stria vascularis to enter the organ of Corti via the endolymph But we are inclined to believe that the conditions prevailing in the mechanism of damage due to a drug are much more complicated

According to Koide (1964) there are at least three routes of kanamycin into the inner ear from the blood vessels (1) the drug enters the endolymph via the stria vascularis (2) the drug passes the blood vessels around the cochlear nerve to reach the organ of Corti via the *perineural spaces* inside the osseous spiral lamina (3) a part of the drug enters the tympanic scala of the basal turn from the round window membrane Therefore if the rate of entrance of the drug via the route inside the osseous spiral lamina is markedly higher inner hair cell damage would precede to outer hair cell damage For this reason the appropriate method of application of the drug to the organ of Corti should be selected if we intend to compare vulnerability of the outer hair cells with that of the inner hair cells

The present investigation was undertaken with three purposes in mind The first was to study the differential vulnerability of the cell population of the organ of Corti to the drug injected in the middle ear cavity It was assumed that a certain amount of the drug will reach the organ of Corti

through the round window membrane (Patterson & Gulick, 1963, 1964, Davis *et al*, 1958, Hennebert & Fernandez, 1959) We think that the local application method may help in studying vulnerability of the hair cells because both the outer hair cells and inner hair cells may be exposed to the same concentration of the drug The second purpose was to study whether the pattern of damage to the cells was almost identical The third purpose was to study correlation between vulnerability of the cells to the drug and histochemical properties of the cells

METHOD

Adult guinea pigs were used as experimental animals Anesthesia was performed with Nembutal, injected intraperitoneally in a dosage of 0 8 ml per kilogram of body weight When a surgical level of anesthesia was reached, the auditory external canal of the left ear was sterilized and the drug solution which was also sterilized, was injected into the middle ear cavity through the tympanic membrane by means of a syringe under an operating microscope The volume of fluid was usually about 0 1 ml Some fluid may have been lost through the Eustachian tube before the drug was entirely absorbed so that the exact dosages were uncertain A time interval of four to seven days between injection and experiments was convenient The following drugs were injected into the middle ear cavity kanamycin sulfate (200 mg per ml), dihydrostreptomycin sulfate (200 mg per ml), chloramphenicol succinate (200 mg per ml), and quinine hydrochloride (saturated solution)

At the final experiment, the animal was sacrificed and the inner ear was taken out The inner ear was stained with the neotetrazolium reagents for succinic dehydrogenase or DPN diaphorase, after removing the round window membrane So the reagents enter the inner ear from this window alone The stained cochlea was decalcified, embedded in gelatine, and cut by a freezing microtome (the routine method) The organ of Corti of the basal turn alone was subjected to observation because damage to the cells may be expected to be localized in the basal turns

RESULTS

A Oxidizing Enzymes in the Organ of Corti Affected by the Drug

The microscopic observations of the 45 antibiotic injected ears showed that kanamycin, dihydrostreptomycin and chloramphenicol produced the identical type of damage to the organ of Corti In 20 ears into which quinine was injected, however, the lesions were more extensive

1 *Changes in the organ of Corti (antibiotic poisoning)*

It is well known that both the outer hair cells and inner hair cells in a healthy animal may be deeply stained by the reagents for the oxidizing

TABLE 1 *Oxidizing enzymes in the hair cells affected by the drugs*

I = Inner hair cell O = Outer hair cell

Enzyme and drug	Number of ears	Number of specimens	*Difference in activity of enzyme*		
			I = O	I > O	I < O
DPN diaphorase					
Kanamycin	9	25	3 (12 %)	22 (88 %)	None
Succinic dehydrogenase					
Kanamycin	12	12	2 (12 %)	10 (82 %)	None
Dihydrostreptomycin	12	43	30 (70 %)	13 (30 %)	None
Chloramphenicol	11	17	4 (23 %)	13 (77 %)	None
Quinine	20	20[a]	11	4[b]	None

[a] Five specimens showed complete necrosis of the organ of Corti

[b] Development of color was poor in all cells of the organ of Corti

enzymes and that development of the color is rather poor in the supporting cells In addition the coloration due to the reagents is deeper in the outer hair cells and to a lesser extent in the inner hair cells as described in the next chapter

In the present experiments, remarkable loss of the oxidizing enzymes was frequently produced in the outer hair cells (Table 1 and Fig 1) It was frequently accompanied by loss of the enzymes in the nerve endings around the basal areas of the outer hair cells However the inner hair cells supporting cells and nerve fibers inside the tunnel of Corti seemed to show no distinct loss of the enzymes compared with the control specimens

Since we could find no specimen in which loss of the enzymes was severe in the inner hair cells and to a lesser extent the outer hair cells it may be said that the outer hair cells are more vulnerable

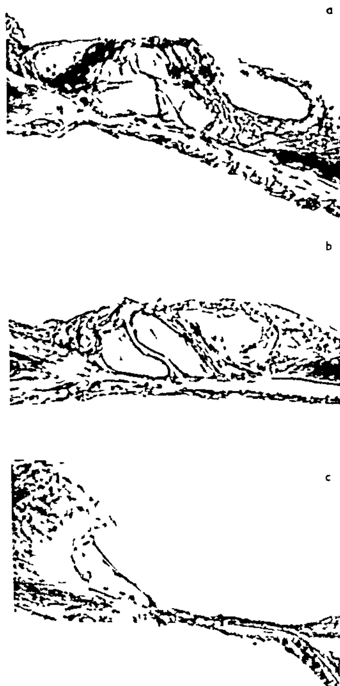
2 *Changes in the organ of Corti (quinine poisoning)*

The lesions were very extensive in the ears into which quinine was injected compared with those of the antibiotic injected ears (Table 1 and Fig 2 Among 20 ears four showed severe loss of the oxidizing enzyme in the whole area of the organ of Corti especially in the outer hair cells (Fig 2 A) However, the inner hair cells and nerve fibers inside the tunnel of Corti preserved a part of the activity of the enzyme It is very interesting that both the outer hair cells and supporting cells shrunk remarkably and became atrophic This finding was a rare occurrence in the ear into which the antibiotic was injected

In 11 ears the degenerative changes in the organ of Corti were more extensive The enzyme became extremely poor in this organ so that both the



FIG. 1. Loss of succinic dehydrogenase of the organ of Corti in the ear into which antibiotic was injected. (A) Kanamycin poisoning. (B) Dihydrostreptomycin poisoning. (C) Chloramphenicol poisoning.



[illegible]. Changes in the organ of Corti affected by quinine. All photomicrographs show loss of succinic dehydrogenase of the organ of Corti, especially the outer hair cells, and atrophy of all cells of this organ.

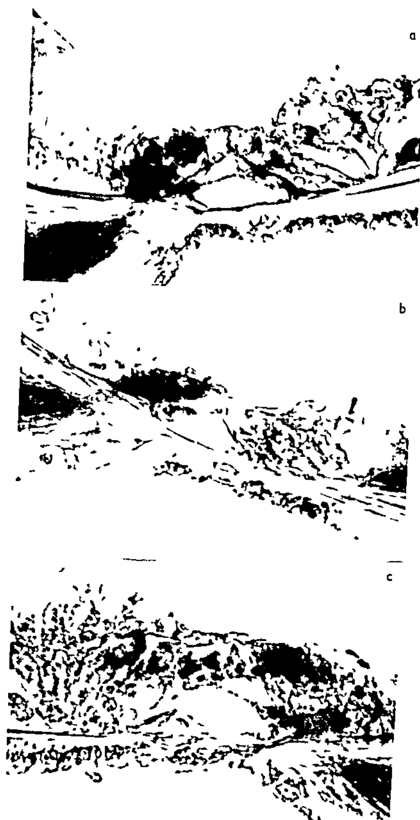


Fig. 1. Loss of succinic dehydrogenase of the organ of Corti in the ear into which antibiotic was injected. (A) Kanamycin poisoning. (B) Dihydrostreptomycin poisoning. (C) Chloramphenicol poisoning.

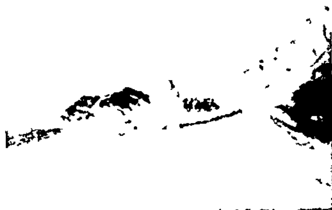


Fig 3 Specimen obtained after short time of incubation in the reagents for succinic dehydrogenase The outer hair cells alone developed deep color while the inner hair cells and Böttcher's cells did not yet show apparent coloration Arrow indicates the Böttcher's cells

cut by a freezing microtome to obtain a specimen about 2 mm in thickness, prior to staining After staining the specimen was decalcified embedded and cut again by a freezing microtome to obtain the final specimens The time of incubation for staining should be controlled under a binocular microscope to avoid over staining Otherwise over staining would interfere with exact comparison of color developed between each cell of the organ of Corti

The important results obtained are summarized in Table 2 This table indicates that activity of succinic dehydrogenase was often higher in the outer hair cells Although the time of incubation for staining was well controlled comparison of activity of the enzyme between the outer hair cells and inner hair cells was difficult to perform in some of the specimens

The observation of the histochemical specimen under a light microscope would give us only qualitative results Thus we cannot distinguish a slight difference in color developed in the cells For this reason we could not in some specimens evaluate whether there was a difference in activity of succinic dehydrogenase between the outer hair cells and inner hair cells However we obtained frequently the fine specimens which showed the deeply stained outer hair cells and the weakly stained inner hair cells if we controlled development of the color in the cells successfully (Fig 3) It should be emphasized that we were not able to obtain a specimen in which the enzyme was rich in the inner hair cells, but poor in the outer hair cells

DPN diaphorase was found to distribute equally in both the inner hair cells and outer hair cells This enzyme was the richest in the nerve endings around the basal areas of the outer hair cells (Fig 4) Both the outer hair

TABLE 2 *Oxidizing enzymes in the hair cells in the control animal*

I = Inner hair cell O = Outer hair cell

Enzyme and method	Number of ears	Number of specimens	Difference in activity of enzyme		
			I = O	I > O	I < O
DPN diaphorase					
Routine method	7	26	26 (100 %)	None	None
Freezing method	12	33	33 (100 %)	None	None
Succinic dehydrogenase					
Routine method	20	37	28 (75 %)	None	9 (25 %)
Freezing method	20	81	30 (37 %)	None	51 (63 %)

outer hair cells and inner hair cells appeared colorless (Fig 2 B). Another five showed complete degeneration of the organ of Corti and replacement by a flat epithelium (Fig 2 C)

Here it should be noticed that the Bottcher's cells were very resistant to quinine They preserved the activity of the enzymes well, even after both the outer hair cells and inner hair cells completely lost activity of the enzyme (Fig 2 A, B) *Similar findings were demonstrated in the ears into* which kanamycin or dihydrostreptomycin was injected As shown in Fig 1 A and B, the Bottcher's cells appeared normal in activity of the enzyme after the outer hair cells were damaged to lose the enzyme

Generally speaking all kinds of drug injections may be said to produce an identical pattern of histochemical changes in the organ of Corti However, we are inclined to think that there is a slight difference in the pattern between antibiotic poisoning and quinine poisoning That is to say, *in the latter cases, slight but distinct loss of the enzyme* was always observed in the inner hair cells and supporting cells when the outer hair cells were damaged to lose markedly the enzyme Such findings were not obtained in the former cases in which the inner hair cells always preserved the enzyme

B Oxidizing Enzymes in the Organ of Corti of the Control Animal

Vosteen (1958) has described that succinic dehydrogenase was rich in the inner hair cells and to a lesser extent, in the outer hair cells According to his report, there was no difference in activity of DPN diaphorase between the outer hair cells and inner hair cells The nerve endings were reported to be rich in succinic dehydrogenase, but poor in DPN diaphorase Our examination concerning distribution of the oxidizing enzymes in the organ of Corti has, however, presented some different results

The specimens were prepared by the routine method But some of them were prepared by the freezing method, where the frozen inner ear was

cells and inner hair cells showed moderate activity of the enzyme, although the nuclei of these cells lacked in this enzyme It is very interesting that succinic dehydrogenase and DPN diaphorase differ in their pattern of distribution (Fig 5) Generally, both the outer hair cells and nerve endings around the basal areas of the outer hair cells seem to be very active in energy production

COMMENTS

The most important result obtained is that the outer hair cells are more vulnerable to the drug compared to the inner hair cells Then a question arises why are the outer hair cells so vulnerable?

Firstly we have called our attention to the biochemical properties of the cells in relation to the vulnerability to the drugs As described above the outer hair cells were found to be richer in succinic dehydrogenase compared to the inner hair cells although DPN diaphorase is distributed equally in both cells This fact suggests that the metabolic activities may be higher in the outer hair cells than the inner hair cells Further it is noticed that DPN diaphorase is the richest in the nerve endings although succinic dehydrogenase is not so rich in them Probably the metabolic activities seem to be higher in the nerve endings than the inner hair cells

Koburg & Plester (1962) have injected amino acids labelled with radio active carbon atoms in to the animal They have found the incorporation of the labelled carbon atoms into the protein to be more apparent in the outer hair cells than the inner hair cells This result also suggests that the metabolic activities are higher in the outer hair cells

Now we are inclined to think that the injurious effects of drugs would well correlate with the metabolic level of the cell In other words the higher the metabolic activities of the cell the easier the occurrence of damage to the cell The experiments done by Hancock (1961) have given us the suggestive results He has explained that the organism may reveal increased resistance to streptomycin during anaerobic growth He has also noticed that the organism becomes very resistant to the drug in the presence of carbon monoxide or 2 heptyl 4 hydroquinoline N oxide (an inhibitor of respiration via the cytochrome system) One cause of the higher vulnerability of the outer hair cells may be the higher rate of uptake of the drug which correlates closely with the higher metabolic activities of the cells as suggested by Hancock

Here another question arises why are the Boettcher's cells very resistant to the drug? It is well known that the activity of succinic dehydrogenase of the cells is very high which appears to be the same as that of the outer hair cells As shown in Fig 1 A and B and Fig 2 A and B frequently the Boettcher's cells were deeply stained with the reagents for the enzyme even after the outer hair cells were damaged to lose the enzyme We can present an interesting finding which seems to facilitate understanding When the

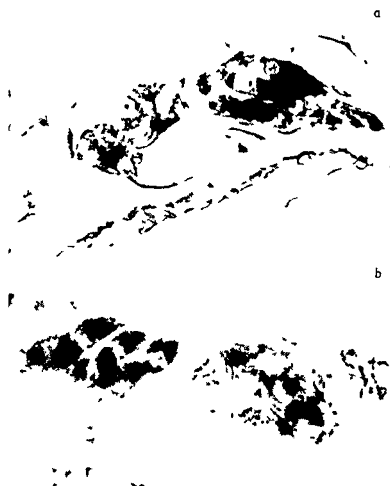


Fig. 4. Distribution of the oxidizing enzymes in the organ of Corti. (A) Distribution of DPN diaphorase. (B) Distribution of succinic dehydrogenase.

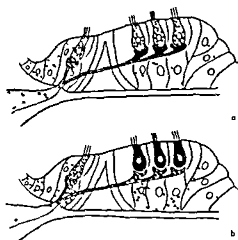


Fig. 5. Schematic representation of distribution of the oxidizing enzymes in the organ of Corti. (A) Distribution of DPN diaphorase. (B) Distribution of succinic dehydrogenase.

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Koburg & Plester (1962) have injected amino acids labelled with radioactive carbon atoms in to the animal They have found the incorporation of the labelled carbon atoms into the protein to be more apparent in the outer hair cells than the inner hair cells This result also suggests that the metabolic activities are higher in the outer hair cells

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Here another question arises why are the Böttcher's cells very resistant to the drug? It is well known that the activity of succinic dehydrogenase of the cells is very high, which appears to be the same as that of the outer hair cells As shown in Fig 1 A and B and Fig 2 A and B, frequently the Böttcher's cells were deeply stained with the reagents for the enzyme, even after the outer hair cells were damaged to lose the enzyme We can present an interesting finding which seems to facilitate understanding When the

time of incubation of the specimen was rather short, as shown in Fig 3 the Böttcher's cells were not frequently stained well, even after the outer hair cells had developed a deep color.

Since no information is available concerning permeability of the basal membrane, we cannot point out the areas of the basal membrane where the drugs are permitted to pass most easily. On the basis of the above finding, one can imagine that the reagents for the enzyme may most easily reach the hair cells through the basal area of the tunnel of Corti and that there is no direct route of the reagents between the Böttcher's cells and tympanic scala Otherwise we cannot explain the weak coloration in this cell. If it is permitted to extend this hypothesis to the problem of resistance of the Böttcher's cells to the drugs, the resistance may be considered to be the phenomenon due to the delayed intoxication That is, the drugs appearing in the tympanic scala firstly reach the hair cells through the basal area of the tunnel of Corti and secondly enter the endolymph to affect the Böttcher's cells

In discussing the problem of vulnerability of the cells, we have to call our attention to the problem of permeability of the cell wall A marked difference in the fine structures of the cell wall would produce a marked difference in uptake of the drug by the cells However, we did not find a marked difference in the structures of the cell wall between the inner hair cells, outer hair cells, and Böttcher's cells in the literature We therefore assume that a slight difference in the morphological structures of these cells may not produce distinct effects on uptake of the drug by these cells In conclusion, the cells with higher metabolic activities seem to be more vulnerable to the drug

Similar results have been obtained by observation of the stria vascularis of animals that received antibiotics systemically The activities of both succinic dehydrogenase and DPN diaphorase of the stria vascularis have been found to be higher in the lower turns (Koide, Hando & Yoshikawa, 1964) Hence it is expected that damage to the stria vascularis due to antibiotic poisoning may be more severe in the lower turns Müsebeck & Schätzle (1962) have examined the toxic effects of dihydrostreptomycin on the ear of guinea pig They have evaluated that histochemical changes in the stria vascularis were more severe in the lower turns That is, succinic dehydrogenase reaction in this tissue was considered as negative in the second turn but positive in the apical turn In addition, the morphological changes in the stria vascularis due to kanamycin poisoning, which seems to be a rare occurrence were more apparent in the lower turns according to our personal experience (Koide) Then the hypothesis that a cell with higher metabolic activities is more vulnerable to a drug seems to apply to the stria vascularis

Weakness of the outer hair cells may also be exhibited in other pathologic processes in the ear As is well known acoustic trauma may be produced in an ear after prolonged application of loud sound, and the de-

generate changes begin in the outer hair cells in this disease. The same finding may be evaluated in the degenerate process in the ear of the shaker mouse (Weber, 1965). At a serious stage of degeneration, the outer hair cells are diminished in numbers, usually in spotty fashion, though the inner hair cells are largely maintained. Several hypotheses concerning the development of cochlear pathology have been presented, but at the present there is no positive evidence for it. But it is believed that the degeneration is triggered off by nutritional deficiency. A further possibility is that higher metabolic activities of the outer hair cells are responsible for weakness of the cell in pathologic processes in the ear.

ZUSAMMENFASSUNG

Die unmittelbaren Wirkungen einiger toxischer Arzneimittel (Kanamycin, Dihydrostreptomycin, Chloramphenicol und Quinin) auf das Cortische Organ wurden an Meerschweinchen untersucht. Das Beschadigungsmuster des Cortischen Organs schien fast identisch zu sein und zeigte die schwerste Degeneration der ausseren Haarzellen sowie Nervenendigungen, welche beide an den Kontrolltieren hohere metabolische Tatigkeiten besassen. Im allgemeinen scheint es wahrscheinlich, dass hohere metabolische Aktivitat der ausseren Haarzellen fur ihre Vulnerabilitat (Schwache gegen pathologische Prozesse) verantwortlich sind.

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HÖRSTÖRUNGEN BEI 802 PATIENTEN MIT FRÜHKINDLICHER HIRNSCHÄDIGUNG

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Unter 802 Patienten mit einer neurologisch gesicherten frühkindlichen Hirnschädigung liegt klinisch in 16,8% eine perzeptive Schwerhörigkeit oder eine Taubheit vor. Allerdings lassen sich nur die audiometrischen Befunde bei 650 normalintelligenten und debilen Patienten (im Unterschied zu den imbezillen und idiotischen Patienten) verwerten, bei denen in 17,8% eine perzeptive Hörstörung zu ermitteln ist.

Noch häufiger kann bei infantilen Zerebralparesen, von denen 323 Patienten beurteilt wurden, eine Hörstörung festgestellt werden (21,4%). Die Häufigkeit perzeptiver Hörstörungen der wichtigsten Formen der infantilen Zerebralparesen stellt sich folgendermassen dar: Hemiplegie 16,7%, Diplegie 20,0%, Tetraplegie 22,8%, Athetose 36,6%, Choreoathetose 40%.

Unter den beurteilten Patienten können 6 verschiedene audiologische Kurvenformen, unabhängig, ob eine infantile Zerebralparese vorliegt oder nicht, nachgewiesen werden: am häufigsten der Hochtonverlust und der lineare Typ, am seltensten der Kuppentyp, Muldentyp, die C-Senke und die Baßschwerhörigkeit. Immer handelt es sich um beidseitige symmetrische perzeptive Hörstörungen.

Die pathologische Hörfunktion infolge frühkindlicher Hirnschädigung verdient besondere Beachtung, da der partielle oder totale Verlust der Hörsphäre enzephalopathischer Kinder in der somatischen Entwicklung erheblich protrahiert.

Die Ansichten über die Genese der perzeptiven Hörstörungen bei Kindern haben sich in den letzten Jahren wesentlich gewandelt. Durch die erweiterte Grundlagenforschung und verfeinerte medizinische Diagnostik treten die hereditären Faktoren zugunsten der erworbenen Hörschädigungen immer mehr in den Hintergrund. Die Untersuchungsergebnisse zahlreicher Autoren (Arnvig 1958, Bordley & Hardy 1951, Getz 1955, Fisch 1955, Bentzen 1959, Soerensen 1958, Zondermann 1959, Beckmann 1960, Kittel & Schmoll-Eskuche 1963) konnten den ursächlichen Wandel, ohne allerdings die frühkindlichen Hirnschädigungen zu berücksichtigen, über die Genese der kindlichen perzeptiven Hörstörungen veranschaulichen.

Für die Entstehung der frühkindlichen Hirnschädigung erscheint es bedeutungsvoll, daß durch die Erweiterung der medizinischen Erkennt-

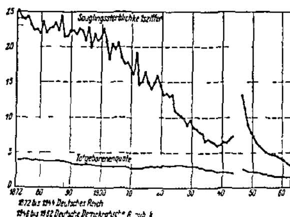


ABB. 1. Säuglingssterblichkeit in den Jahren 1872–1963 nach Reimann.

nisse in den letzten Jahrzehnten die Säuglingssterblichkeit erheblich gesenkt wurde (Abb. 1). Obwohl der größte Teil der überlebenden Säuglinge die verschiedensten früher tödlich verlaufenden prä-, peri- und postnatalen Erkrankungen komplikationslos übersteht, ist bei einem geringeren Teil mit einer Defektheilung zu rechnen. Exakte statistische Hinweise auf die Häufigkeit frühkindlicher Hirnschädigungen finden sich in der Literatur nicht.

Die frühkindlichen Hirnschädigungen besitzen eine zunehmende Bedeutung für zahlreiche Fachdisziplinen. Nach unseren Untersuchungen ist, entsprechend der absinkenden Säuglingssterblichkeit, mit einer vorläufig noch nicht prozentual einschätzenden Zunahme von perzeptiven Hörstörungen infolge frühkindlicher Hirnschädigungen zu rechnen.

Beschreibungen von Hörstörungen bei neurologisch gesicherten frühkindlichen Hirnschädigungen, abgesehen von allgemeinen Angaben über die Häufigkeit von perzeptiven Schwerhörigkeiten bei infantilen Zerebralparesen, sind uns aus der Literatur nicht bekannt. Die Hinweise verschiedener Autoren (Phelps, 1962, Sedlacková & Simek, 1952, Fisch, 1955, Cardwell, 1959, Porter, 1959, Bentzen, 1959, Barr & Klockhoff, 1959, Fricker & Petermann, 1962) über die Hörstörungen bei infantilen Zerebralparesen liegen zwischen 7 und 90%. Einmütigkeit besteht nur darin, daß die Athetosen am häufigsten mit Hördefekten einhergehen. Deshalb glauben wir berechtigt zu sein, unsere klinischen und audiologischen Erfahrungen bei enzephalopathisch geschädigten Patienten ohne und mit infantilen *Zerebral*paresen, mitzuteilen.

PATIENTENGUT UND METHODIK

Wir überblicken ein Patientengut von 802 prä-, peri- und postnatal enzephalopathisch geschädigten Kindern und Erwachsenen, bei denen die Diagnosen von neuropsychiatrischen, kinderneuropsychiatrischen und pädiatrischen Einrichtungen gestellt wurden. Der klinische Befund einer frühkindlichen Hirnschädigung konnte durch eine elektroenzephalogra-

phische, pneumoenzephalographische, feinmotorische und psychologische Beurteilung gesichert werden

Unser Krankengut enthält sowohl männliche als auch weibliche Patienten zwischen dem 3 und 63 Lebensjahr, in der Mehrzahl jedoch schulpflichtige Kinder Eine Auswahl der Patienten nach bestimmten Gesichtspunkten wurde nicht getroffen Wir untersuchten sie ohne Berücksichtigung der uns interessierenden Hörstörungen Bewußt erfolgten keine Beurteilungen hirngeschädigter Patienten in Schwerhörigen- und Gehörlosenschulen Unser Patientengut enthält neben 313 normalintelligenten Patienten 337 Fälle mit Debilität, 109 mit Imbezillität und 43 mit Idiotie

Wir führten bei allen normalintelligenten und debilen Patienten eine Schwellenaudiometrie durch Diese Methode eignet sich aus verständlichen Gründen nicht bei imbezillen und idiotischen Patienten Deshalb mußten hier orientierende Hörprüfungen erfolgen Verwendung fanden tiefe und hohe Hupensignale in verschiedenen Lautstärken Geräusche mit der Baranyschen Lärmtrommel und Stimmgabeltöne Des weiteren erlaubten binaurale Hörprüfungen auf Satzverständnis allgemeine Rückschlüsse auf das Hörvermögen

Obwohl neben schwellenaudiometrischen Untersuchungen, die bekanntlich nur eine periphere Diagnostik erlauben, zentrale Hörteste sicher von großem Interesse gewesen wären, sahen wir davon ab Die Gründe liegen einerseits in der z Z noch mangelhaften Methodik und Einschätzung der Befunde (Matzker, 1960, 1964, Oeken 1962) und andererseits in der großenteils vorliegenden motorischen Unruhe mit Kontaktarmut und den zahlreichen Intelligenzdefekten unserer hirngeschädigten Patienten Bei der Besprechung unserer Ergebnisse soll bewußt der Begriff „Innenohrschwerhörigkeit" vermieden und von perzeptiven Hörstörungen gesprochen werden An dieser Stelle sei betont, daß bei den nachfolgend beschriebenen Hörstörungen hereditäre Faktoren immer ausgeschlossen werden konnten und Schalleitungsschwerhörigkeiten nicht mit bewertet wurden

ERGEBNISSE UND DISKUSSION

Bei 135 (16 8%) von unseren 802 Patienten sind unterschiedlich ausgeprägte Hörstörungen festzustellen Die Tabelle 1 soll über die Verteilung der Hördefekte nach ihren Ursachen (prä, peri und postnatal) unter schematisierender Einteilung in leichte mittlere und hochgradige Hörschädigung sowie Taubheit informieren

Bezüglich der verschiedenen soweit eruierbaren, exogenen Ursachen sei festgestellt daß Hörstörungen infolge Morbus haemolyticus neonatorum (ohne Austauschtransfusion), Frühgeburt und tuberkulöser Meningitis am zahlreichsten nachweisbar sind Über nähere Einzelheiten soll in einer späteren Mitteilung berichtet werden

Wie bereits erwähnt, konnte in Abhängigkeit vom Intelligenzgrad nur ein Teil der Patienten exakt audiometrisch beurteilt werden Um die mit

TABELLE 1. *135 Perzeptionsdefekte bei 802 Patienten mit frühkindlicher Hirnschädigung mit und ohne infantile Zerebralparese*

		Hörschädigung			
	Gesamtzahl	leichte	mittlere	hochgrad.	Taubheit
pränatal	64	8	3	4	4
perinatal	379	17	16	17	5
postnatal	156	13	6	2	8
Ursache unbekannt	203	20	6	1	2
Insgesamt	802	58	31	27	19
			135		

Sicherheit diagnostizierten akustischen Perzeptionsdefekte von den mittels orientierenden Hörprüfungen angenommenen Hörstörungen zu trennen, muß eine summarische Aufteilung in 2 Gruppen vorgenommen werden.

Einmal handelt es sich um 650 normalintelligente und debile Patienten, bei denen in 116 Fällen perzeptive Hörstörungen (17,8 %) und um 152 imbezille und idiotische Patienten, bei denen in 19 Fällen (= 12,5 %) perzeptive Hörstörungen ermittelt werden konnten. Unsere Ergebnisse bei den imbezillen und idiotischen Patienten möchten wir nur mit größter Zurückhaltung mitteilen. Mit hoher Wahrscheinlichkeit ist die Anzahl der perzeptiven Hörstörungen bei dieser Patientengruppe höher, ohne daß eine methodische Erfassung mit den derzeit bekannten Untersuchungsmöglichkeiten gelingt.

Eine weitere Einteilung unserer 802 Patienten kann in frühkindliche Hirnschädigungen *ohne* infantile Zerebralparese (479 Fälle) und *mit* infantiler Zerebralparese (323 Fälle) erfolgen. Setzt man die 479 Patienten ohne infantile Zerebralparese zu den nachweisbaren perzeptiven Hörstörungen in Beziehung, so kann bei 66 Patienten (= 13,8 %) eine Schwerhörigkeit bzw. Taubheit festgestellt werden. Dagegen ist bei den 323 Patienten mit infantiler Zerebralparese eine größere Anzahl von Hörstörungen zu ermitteln. *Es lassen sich unter diesen Patienten 69 Fälle* (= 21,4 %) mit Schwerhörigkeit bzw. Taubheit nachweisen. Diese Befunde sind verständlich, da bei den infantilen Zerebralparesen, den sogenannten „Spastikern", der neurologische Befund wesentlich ausgeprägter ist und die Schädigung des Zentralnervensystems größere Bezirke umfaßt.

Einen genaueren Überblick über die Häufigkeitsverteilung der Hörstörungen bei infantilen Zerebralparesen unter Einbeziehung der verschiedenen Lähmungstypen vermittelt Tabelle 2. Wenn man von den nur vereinzelt auftretenden Formen der infantilen Zerebralparese absieht, kann man erkennen, daß die Hemiplegie am seltensten (16,7 %) und die Choreoathetose am häufigsten (40,0 %) von einer Hörstörung begleitet ist.

TABELLE 2 *Häufigkeit der perzeptiven Hörstörungen bei den einzelnen Formen der infantilen Zerebralparese*

Form der infantilen Zerebralparese	Patientenzahl	Häufigkeit der Hördefekte	
Hemiplegie	112	18	16,7 %
Diplegie	70	14	20,0 %
Tetraplegie	79	18	22,8 %
Athetose	30	11	36,6 %
Choreoathetose	10	4	40,0 %
Ataxie	6		
Monoplegie	5		
Suprabulbarparalyse	4		
Chorea	4	3	
Tremor	1		
Hemiballismus	1		
Torsionsdystonie	1	1	
Insgesamt	323	69	21,4 %

Audiometrische Untersuchungen erfolgten lediglich bei normalintelligenten und debilen Patienten. Die Befunde ergaben, abgesehen von den unterschiedlichen Schweregraden (*leichte Perzeptionsschwerhörigkeit bis zur Taubheit*), keineswegs immer den gleichen Kurvenverlauf.

Prinzipiell lassen sich mit der Schwellenaudiometrie 6 verschiedene Kurvenformen erkennen (Abb. 2). Zu betonen ist, daß kein Kurventyp einseitig nachweisbar ist; stets handelt es sich um beidseitige, symmetrische Hörverluste.

Trotz der großen Anzahl der von uns durchgeführten audiometrischen Untersuchungen sind Beziehungen der einzelnen Kurvenformen zu den prä-, peri- und postnatalen Ursachen nicht sicher aufzustellen.

Im einzelnen unterscheiden wir den Kuppentyp, den Muldentyp, die Baßschwerhörigkeit, den Hochtonverlust, die C^5-Senke und den linearen Typ.

In jedem Fall haben diese Schwerhörigkeiten perzeptiven Charakter. Ausgeprägte Hörverluste sind bei den ersten 3 Kurventypen nicht zu beobachten. Dagegen können die 3 letzten Typen sämtliche Schweregrade einer Hörstörung aufweisen.

Bei unseren 650 normalintelligenten und debilen Patienten verteilen sich die audiometrisch nachweisbaren 116 perzeptiven Hörstörungen neben der Taubheit (11 Fälle) auf die 6 verschiedenen audiologischen Kurvenformen unterschiedlich.

Am häufigsten können bei unseren Patienten „Hochtonverluste" sämtlicher Schweregrade, die in ihrer Verlaufsform eine Ähnlichkeit mit der Presbyakusis haben, beobachtet werden (58 Fälle). Neben geringen Hörverlusten in den höchsten Frequenzen bestehen ausgeprägte Hördefekte,

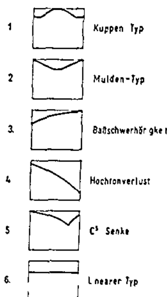


Abb. 2. Schematische Darstellung der verschiedenen audiometrischen Kurvenformen

wobei nur noch Hörreste vorhanden sind. Bentzen (1959), Beckmann (1960), Kittel & Schmoll-Eskuche (1963) bringen diese Hochtonverluste („high tone loss") mit einer Anoxie unter der Geburt in Beziehung. Wir können diese Kurvenform nicht nur bei perinatalen, sondern auch bei prä- und postnatalen Hirnschädigungen sehen.

Am zweithäufigsten findet sich unter unseren hirngeschädigten Patienten audiologisch der „lineare Typ" (32 Fälle). Dabei lassen sich die unterschiedlichsten Schweregrade, vom leichten bis zum hochgradigen Hörverlust, ermitteln.

Die von Helmer (1954), beschriebene audiologische Kurvenform bei multipler Sklerose kann nach unseren Untersuchungen auch bei frühkindlichen Hirnschädigungen nachgewiesen werden (9 Fälle). Dabei handelt es sich nur um leichte Hörverluste, besonders der unteren und oberen Frequenzen, zwischen 30 und 40 dB. Die mittleren Frequenzen entsprechen fast immer dem normalen Hörvermögen. Dieser „Kuppentyp" ist unter unseren Patienten mit Hörstörungen selten.

Ein weiterer seltener Kurventyp bei frühkindlichen Hirnschädigungen ist der „Muldentyp", den Franz (1963), vorwiegend bei hereditären Hörstörungen beobachtet hat. Hier kann bei annähernd normalem Hörvermögen der tiefen und hohen Frequenzen eine leichte Hörstörung in den mittleren Frequenzen auftreten.

Im Zusammenhang mit der Baßtaubheit machten Gravendeel (1958), Langenbeck (1963, 1964) und Ganz (1964) in der letzten Zeit auf die „Baßschwerhörigkeit" aufmerksam und betonten die Seltenheit von Hörstörungen in den tiefen Frequenzbereichen. Während diese Autoren den Kurventyp bei einseitigen, apoplektiformen Erkrankungen des Innenohres u. a. beschreiben, ist die Baßschwerhörigkeit bei unseren Patienten stets beidseitig vorhanden (2 Fälle).

Audiologisch lassen sich bei weiteren 2 Patienten „C⁵ Senken" nachweisen wie sie als Folgen eines Larm oder Schadeltraumas bekannt sind

Hervorzuheben ist daß Schlußfolgerungen anhand unserer audiometrischen Befunde auf eine stattgefundene fruhkindliche Hirnschädigung aus verstandlichen Grunden nur unter Einbeziehung weiterer klinischer Ergebnisse möglich sind

SUMMARY

Of 802 patients with infantile brain damages proved neurologically 16 8% have a perceptive hardness of hearing or deafness Only in 650 cases however, consisting of normal intelligent and weak patients (contrasting with the imbecile and idiotic patients) the audiometric findings are of use, in 17 8% a perceptive hearing damage was found

Even more frequent hearing damages may be stated in infantile cerebral paresis 323 patients of which were examined (21 4%) The frequency of perceptive hearing damages concerning the most important forms of infantile cerebral paresis is stated in per cent as follows hemiplegia 16 7%, diplegia 20 0% tetraplegia 22 8%, athetosis 36 6%, choreoathetosis 40%

Of the examined patients 6 different audiological sorts of curves may be pointed out independent of whether an infantile cerebral paresis exists or not most frequent high tone loss and the linear type most rarely the head type (hearing loss in the higher and lower frequencies with remaining frequencies in the middle) the trough shaped type the c⁵-dip and the bass deafness All of them are bilateral symmetric perceptive hearing damages

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OTOSCLEROSIS IN SOUTH INDIA

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There is very little information available on the racial distribution of otosclerosis The incidence of otosclerosis in South India among Dravidians is high The incidence of otosclerosis among all patients with hearing loss seen at the Christian Medical College Hospital Vellore in 1962 and 1963 was 30% and 31% respectively The South Indians are not the original inhabitants of India They are migrants from Eastern Europe and the Middle East Comparisons were made with other studies on otosclerosis as regards the incidence sex and age distribution the onset and duration of hearing loss and clinical features of otosclerosis in this region

Very little is known about the racial incidence of otosclerosis Guild (1950) stated that otosclerosis is not rare in Caucasians and that nothing is known about its incidence in the yellow races of mankind or in any of the undiluted black races A study was undertaken to determine the incidence of otosclerosis among patients attending the Christian Medical College Hospital Out patients with complaints of difficulty in hearing

Otosclerosis was found to be a common cause of hearing loss in South India This high incidence of otosclerosis in South India is surprising for the Dravidians who form the major part of the population of South India have been regarded as an old and primitive race not likely to have this disease However a review of the history of the people of South India suggests that they have a varied origin many of them originating in European and Middle Eastern regions The people of India according to physical type and language can easily be distinguished into two broad classes They are the Aryans who live in the North and the people living in the South Indian peninsula whose features and language are quite different from the Aryans These people are called by the generic name of Dravidians

Nilakanta Sastri (1958) who has studied the racial composition of the people of South India has divided them into several groups

1 *Negrito* The negrito is a diminutive type of negro who originating in Africa like the negro passed through India eastward and is found in the Andaman Islands in the Indian Ocean

2 *Proto Australoid* The proto Australoid has a long head with protruding face broad flat nose and a pronounced brow ridge

3 *Proto Mediterranean* The distinguishing features of this type are long narrow head and face nose of medium length straight and aquiline and

dark brown hair. This is the dominant type among Dravidian people in South India today.

4. *Mediterranean.* In South India the dominant characteristics of this type are slender build, short to medium height, long head, small browridge, oval face, and usually, a pointed chin. It seems that this type did not derive from the proto-Mediterranean type in India, but is an imported strain.

5. *Armenoid.* This type, which may have originated in south west Asia is short-headed, having a markedly convex, high-bridged nose, and a high vaulted head, which rises steeply from the nape of the neck.

6. *Nordic.* The Nordic, another progressive long-headed element, entered South India in prehistoric or proto-historic times. Having come from the same original stock, the Mediterranean and Nordic have similar head shapes. Whereas the Mediterranean skull is small, the Nordic is massive. In South India, the largest percentage of this group is among the Tamil Brahmins.

Thus the Dravidians are composed of Negroid, Mediterranean, Middle Eastern, and Nordic stock. From this it is evident that the Dravidian race, contrary to general impression, cannot be called a primitive race.

Another feature which may have a bearing on the high incidence of otosclerosis in South Indians is the marriage customs. Most Tamilians choose spouses mainly from their castes, especially from their own relatives. This is done for reasons of economic security. A study of the histories of over 1000 children in Vellore (Kapur, 1966) shows that 34% parent marriages are consanguineous. These are uncle–niece and first cousin marriages. If distant relative marriages are included, the incidence of consanguineous marriages rises to 40–45%.

PRESENT STUDY

A two-year study was made of the number of patients having otosclerosis who attended the Ear, Nose, and Throat Clinic of the Christian Medical College Hospital, Vellore, South India, during 1962 and 1963 (Table 1). Of all patients diagnosed as having "hearing loss" during this period in 1962 30% of the patients had otosclerosis. The corresponding figure for 1963 was 31%. The incidence may be even higher, for undoubtedly many patients do not come for diagnosis and treatment for economic reasons.

In this study the diagnosis of otosclerosis was made if the patient complained of unilateral or bilateral hearing loss of insidious onset, progressive in nature, and unaccompanied by otalgia or otorrhea. The otological examination disclosed normal tympanic membranes, and audiometry revealed a conductive hearing loss.

The sex distribution is given in Table 2.

The number of patients having tinnitus, hearing loss, unilateral or bilateral, and the number in which the diagnosis was confirmed by tympanotomy are given in Table 3.

TABLE 1 *Number of patients with hearing loss due to otosclerosis and hearing loss due to other causes seen in 1962 and 1963*

	1962	1963	Total
Cases attending E N T Out patients with hearing loss	671 (100 %)	685 (100 %)	1356 (100 %)
Otosclerosis cases	203 (30.3 %)	211 (30.8 %)	414 (30.5 %)

TABLE 2 *Sex distribution of cases with otosclerosis and those with hearing loss due to other causes*

	Otosclerosis cases	Hearing loss due to other causes	Total
Males	292 (70.5 %)	653 (69.3 %)	945 (69.7 %)
Females	122 (29.5 %)	289 (30.7 %)	411 (30.3 %)
Total	414 (100 %)	942 (100 %)	1356 (100 %)

TABLE 3 *Analysis of the symptoms and findings in cases of otosclerosis*

	1962			1963			Total		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
Otosclerosis cases	148 (72.9 %)	55 (27.1 %)	203 (100 %)	144 (68.3 %)	67 (31.7 %)	211 (100 %)	292 (70.5 %)	122 (29.5 %)	414 (100 %)
Cases confirmed by operation	90	35	125 (61.6 %)	98	44	141 (66.8 %)	188	78	266 (64.3 %)
Cases not operated	58	20	78 (38.4 %)	46	24	70 (33.2 %)	104	44	148 (35.7 %)
Tinnitus present	95	35	130 (64.0 %)	112	55	167 (79.1 %)	207	90	297 (71.7 %)
Tinnitus absent	53	20	73 (36.0 %)	32	12	44 (20.9 %)	85	32	117 (28.3 %)
Unilateral hearing loss	10	0	10 (4.9 %)	7	1	8 (3.8 %)	17	1	18 (4.3 %)
Bilateral hearing loss	138	55	193 (95.1 %)	137	66	203 (96.2 %)	275	121	396 (95.7 %)

REVIEW OF THE LITERATURE

According to Altmann (1961), clinical experience seems to indicate also that in the yellow race otosclerosis is much less common than in the white race

In a random selection of 170 of their patients with otosclerosis, Joseph & Fraser (1964) found that the disease was twice as common among the Caucasians as in the Japanese. The authors felt that in this group each ethnic group was well represented

Mawson (1963) states the incidence of otosclerosis in the general population in the western hemisphere approximates to at least one in 200

Shambaugh (1949) stated that clinical otosclerosis affects perhaps 0,5% to 1% of white adults, although he admitted that no exact statistics of its incidence are available.

Nylen & Nylen (1952) quote Fowler, Jr.'s opinion that a fair estimate of otosclerosis in the white race would be nearer to 10% for males and 20% for females if undetected or "potential" otosclerosis were included

Guild (1944) studied 1161 temporal bones, which were almost equally divided between Whites (585) and Negroes (576) in the United States, and found histologic otosclerosis in forty-nine or 4 22% of the cases He found the racial incidence of otosclerosis to be 1 in 12 for the Whites and 1 in 96 for the Negroes The incidence he found for sexes was 1 in 8 for females and 1 in 15 for males

Engström (1940) examined 145 temporal bones of 100 nonselected individuals and found otosclerotic lesions in twelve.

Unilateral histologic otosclerosis was observed in 25% of Guild's (1944) cases, 26% in Fleischer's (1957–1958) cases and 15–30% in Nylén's (1949) cases

Fleischer's (1957–1958) series consisted of 98 temporal bones of 68 patients Nylen examined 74 cases histologically (121 otosclerosic bones) and found unilateral otosclerosis in 15–30% in his cases

Hoople (1952) found the incidence if unilateral otosclerosis as high as 10%

Larsson (1960) found unilateral otosclerosis in 15% of his cases

Shambaugh (1959) reports that many observers have noted a definite sex incidence, otosclerosis being approximately twice as frequent in women as in men In 2000 consecutive fenestration operations that he performed, 68 7% were on women and 31 3% on men

Shambaugh (1959) found a hereditary tendency in 54 4% of his series of 2000 otosclerotic cases The opinion that there is a hereditary tendency is strengthened by the occurrence of otosclerosis in identical twins as reported by Shambaugh (1935) (three sets of twins), and Fowler (1947) (five sets of twins) Shambaugh (1959), however, states that otosclerosis is not invariably present in both twins, for Fowler (1947) and Juers (1950) have each reported an instance in which only one twin was affected

According to Shambaugh (1959) the true hereditary tendency toward otosclerosis will be established only when each member of families, in which someone has clinical otosclerosis, is studied histologically

Cawthorne (1955) analysed 2000 adults, who attended a Hearing Aid Distribution Center to obtain hearing aids, and discovered that 944 (47%) had clinical otosclerosis He concluded that otosclerosis is the commonest cause of hearing loss in the adult, and that its incidence is not less than one-half per cent of the population In his series, the sex incidence was 67 5% females and 32 5% males In his series of 2000 cases he found unilateral hearing loss in 3 5% cases (71 cases out of 2000 cases)

According to Larsson (1961) there is a higher proportion of females among otosclerosis patients who seek medical advice, while among unselected cases no sex difference can be found

Larsson (1961) assumes that the degree of manifestation of clinical otosclerosis is between 15 and 30% By using Guild's material and the Hardy Weinberg method of calculation he arrives at this conclusion In a clinical analysis of 318 cases he shows that the risk period comprises the eleven to 45-year age group In his series a positive family history was obtained in 49% of cases tinnitus occurring in 76% 15% had unilateral otosclerosis

Ricci (1961) declares that genetic studies in otosclerosis patients are difficult because of the recessive character of hereditary transmission This characteristic causes the disease to remain latent for several generations then to be transmitted by apparently healthy individuals The impossibility of tracing a complete family history presents another difficulty

DISCUSSION

That otosclerosis is a common cause of hearing loss in the Dravidian population of South India is seen from the study of 414 otosclerosis patients in the two year period of 1962 and 1963 Of all patients complaining of hearing loss 30% were diagnosed as having otosclerosis *There are no figures available that show* the incidence of clinical otosclerosis in the general population of north or south India The sex incidence of otosclerosis in India is much more for men than women In this series, 73% of all otosclerosis patients in 1962 were men and 68% in 1963 were men This is in contrast to the general accepted view that otosclerosis is more common in women than in men

Sex distribution of otosclerosis in this series may not present the true picture, for many women do not come to the hospital for treatment In India man is the bread-earner and the important person of the family Unless absolutely necessary, women do not usually come for treatment This is indicated in Table 2 Comparison of the number of men and women attending the clinic for hearing loss other than otosclerosis showed that in the two year period (1962 and 1963) 69% were men and 31% were women The diagnosis of otosclerosis was confirmed by operation in 64% of all patients studied in this series (Table 3) Tinnitus was present in 72% of the cases Unilateral loss was found in 4% of the cases (Table 3)

The age distribution of all hearing loss patients attending the clinic is tabulated in Table 4 Otosclerosis seems to be more prevalent in patients between fifteen and thirty nine years 80% of the cases were in the age group of 15–39 years The youngest in this series was a 8 year-old girl and the oldest a 72 year old man

Table 5 gives the duration of hearing loss before patients came to the hospital for treatment This can be anywhere between one year (17%) and 41 years (0 2%) The largest group (34%) of patients had a hearing loss of 2 to 4 years duration

No attempt has been made to give any figures of the hereditary tendency of otosclerosis in this study It has been the experience here that invariably a family history of hearing loss is not forthcoming Some patients feel that admission of such a defect in the family is a stigma and it is best to deny

TABLE 4 *Table showing the age distribution of cases with hearing loss due to otosclerosis and all cases of hearing loss seen in E N T clinic*

Age group (year)	Cases attended E N T Outpatients with hearing loss				Otosclerosis cases			
	1962	1963	Total	(%)	1962	1963	Total	(%)
0–4	25	14	39	(2 9)	0	0	0	(0 0)
5–9	63	46	109	(8 0)	1	0	1	(0 2)
10–14	53	45	98	(7 2)	4	3	7	(1 7)
15–19	65	101	166	(12 2)	19	28	47	(11 4)
20–24	120	95	215	(15 9)	45	40	85	(20 5)
25–29	77	76	153	(11 3)	31	45	76	(18 4)
30–34	69	93	162	(11 9)	25	43	68	(16 4)
35–39	55	66	121	(8 9)	27	29	56	(13 5)
40–44	57	50	107	(7 9)	27	13	40	(9 7)
45–49	30	25	55	(4 1)	11	5	16	(3 9)
50–54	16	28	44	(3 2)	7	2	9	(2 2)
55–59	19	14	33	(2 4)	3	2	5	(1 2)
60–64	10	13	23	(1 7)	1	0	1	(0 2)
65–69	3	9	12	(0 9)	1	0	1	(0 2)
70–74	6	8	14	(1 0)	1	1	2	(0 5)
75–79	3	2	5	(0 4)	0	0	0	(0 0)
Total	671	685	1356	(100)	203	211	414	(100)

it In other cases the patients, being illiterate, cannot give accurate information Under these circumstances no figures on the hereditary tendency of otosclerosis in the patients examined are given Hereditary, it is felt, does contribute to the high incidence of otosclerosis in this region because as

TABLE 5 *Duration of hearing loss at the time the otosclerosis patients came to the hospital*

Duration (years)	Number of otosclerosis cases			
	1962	1963	Total	(%)
Up to 1 year	31	41	72	(17 4)
2–4	62	78	140	(33 8)
5–9	55	46	101	(24 4)
10–14	26	27	53	(12 8)
15–19	6	14	20	(4 8)
20–24	19	4	23	(5 6)
25–29	1	1	2	(0 5)
30–34	1	0	1	(0 2)
35–39	1	0	1	(0 2)
40–44	0	0	0	(0 0)
45–49	1	0	1	(0 2)
Total	203	211	414	(100)

many as 34% of the marriages in this region are consanguineous marriages (Kapur 1966)

A number of cases who have otosclerosis do not come to hospital for economic reasons These cases do not seek treatment unless the hearing loss interferes with their capacity to continue in their work The majority of the people in this region are farmers, who do not find a mild or moderate hearing loss a handicap If all these cases were to come to hospital for treatment the incidence of otosclerosis would be very much higher A survey of the incidence of otosclerosis in the general population in this area is needed

ZUSAMMENFASSUNG

Über die Verbreitung der Otosklerose in bezug auf Rassen ist sehr wenig Material vorhanden In Südindien ist die Anzahl von Otoskleroseſällen bei den Drawiden hoch Bei den Patienten mit Hörverlust die im Christian Medical College Hospital in Vellore in den Jahren 1962 und 1963 untersucht wurden betrugen die Otoskleroseſälle 30 bzw 31% Die Südindier sind nicht die ursprünglichen Einwohner Indiens sondern von Osteuropa und dem Mittleren Osten eingewandert

Vergleiche mit anderen Untersuchungen über Otosklerose wurden vorgenommen in bezug auf ihr Vorkommen Verteilung auf Alter und Geschlecht Beginn und Dauer des Hörverlustes und die klinischen Merkmale der Otosklerose in diesem Gebiet

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RECORDING OF CRANIO LABYRINTHINE PRESSURE TRANSMISSION IN MAN BY ACOUSTIC IMPEDANCE METHOD

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This investigation shows that an increase in intracranial pressure produced by compression of the cervical veins regularly produces changes of the acoustic impedance of the middle ear Observations in man and experiments on the cat and guinea pig indicate that these impedance changes are caused by transmission of hydrostatic pressure to the labyrinthine fluids and a consequent increase in the mechanical load on the stapedial footplate

Preliminary attempts to use the method for diagnostic purposes in five unilateral cases of Meniere s disease and in one case of acoustic neurinoma were negative the impedance responses to the increase in intracranial pressure being equal bilaterally and of the same magnitude as in normal subjects

The anatomical background of cranio labyrinthine pressure transmission is discussed with particular reference to cases of excessive cerebrospinal fluid leakage occasionally observed in stapes surgery and rare cases of spontaneous fluctuations of the acoustic impedance of the middle ear

The phenomenon reported may partly explain the difficulties encountered in demonstrating significant pathological values when absolute acoustic impedance measurement is applied in the diagnosis of middle ear disease

An introduction to the extensive literature on the circulation of the labyrinthine fluids can be found in the monograph edited by Rauch (1964) Earlier reviews have been presented by Werner (1940) F Kobrak (1949) Altmann & Waltner (1950) and Lempert *et al* (1952) Recent research in this field has provided information concerning the electrolyte composition and the formation of these fluids (cf Rauch 1964) The scope of the present study is restricted to the interaction between the hydrostatic pressures of the cerebrospinal fluid and the labyrinthine fluids

In animals it has previously been shown by several investigators that the hydrostatic pressure of the cerebrospinal fluid is readily transmitted to the fluids confined within the otic capsule namely, the perilymph and endolymph The hydrostatic pressure of the inner ear fluids has been studied by means of various types of capillary manometers (Szasz 1926 Hughson 1932 H Kobrak 1933) by visual observation (Ahlen 1947) or

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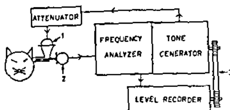


FIG 1 Schematic representation of the equipment used in the animal experiments *1* Sound source *2* condenser microphone with sound probe *3* mechanical drive from the level recorder to the frequency control of frequency analyzer and tone generator

operating at 25 c band width and recorded on a level recorder (Bruel & Kjaer type 2305) equipped with a 50 dB logarithmic potentiometer Records were made using the motordriven continuous frequency sweep of the wave analyzer operating between 0 2 kc and 12 kc A frequency sweep was made before and during experimentally produced impedance changes The difference between the two curves thus represented the change in sound pressure at the tympanic membrane due to the impedance change In order to study the time course of the response measurements were made with the carrier tone fixed at the frequnency found to give the optimal response

In the experiments on man an increase in intracranial pressure was produced by compressing the cervical veins by means of an ordinary blood pressure cuff applied around the neck of the subject The cuff was manually inflated at an approximately uniform rate to give a cuff pressure of 30 mm Hg in about 15 seconds The pressure was maintained at this level for about 10 seconds and subsequently raised to 50 mm Hg after which the cuff pressure was released None of the subjects found this procedure painful In some cases a slight discomfort was noted when the pressure was raised above 30 mm Hg but no signs of alarming circulatory disturbances were observed

In the *animal experiments the head was fixed in a rigid holder and the* bony part of the external auditory meatus was exposed surgically to provide a firm and tight connection with the impedance recording device The bulla was opened to eliminate any possible changes of middle ear pressure during the experiment and to allow inspection under the dissecting microscope An increase in intracranial pressure was produced in the same way as in the human experiments or by injecting Ringer solution through a cannula inserted through the atlanto-occipital membrane the pressure applied being followed by means of a water manometer As soon as the injection was discontinued the pressure decreased fairly rapidly indicating that the increase in volume was gradually eliminated from the cranial cavity (Davson 1956) The injections could be repeated 5–10 times in each animal without any irreversible changes in the pressure response or the general condition of the animal being noted

recording of the movements of the round window membrane (Filippi, 1950 Krejci & Bornschein, 1951). Because of the necessity for a surgical operation in the application of these methods, similar studies *in vivo* have not been made in man.

There is, however, another approach to this problem Since a change in the hydrostatic load on the round window membrane will result in a change in the load on the stapedial footplate, it would be expected to affect the acoustic impedance of the middle ear The present investigation shows that this is true and a technique for continuous recording of middle ear impedance changes, previously used for study of middle ear muscle reflexes *in man* (Klockhoff, 1961), was found to be a convenient method for observing the effect of experimentally induced changes in intracranial pressure on the pressure of the inner-ear fluids Short communications on the results in this paper have previously been published (Klockhoff, Änggård & Änggård, 1964 *a*, 1964 *b*)

MATERIAL AND METHODS

Experiments were performed on normal human subjects and on cases of certain middle and inner ear diseases In an additional investigation on animals, experiments were performed on anesthetized cats (vet *Nembutal*®, 35–40 mg/kg b w) and guinea pigs (20 per cent urethane solution, 8 ml/kg b w) A more detailed presentation of the material is given below in the sections dealing with the findings in the different experimental groups

For continuous recording of middle ear impedance changes in man an electroacoustic equipment was employed, the principal features of which have been described by Klockhoff & Anderson (1959) and in greater detail by Klockhoff (1961) This technique is founded on the fact that the evoked changes in impedance affect the reflection of a carrier tone directed towards the tympanic membrane via a probe inserted into the external auditory canal The resulting change in sound pressure is measured with a frequency selective voltmeter and recorded with a logarithmic writer

In the animal experiments a modified but similar technique was used The device by means of which the sound source for the carrier tone and the measuring microphone were connected to the external auditory meatus is shown schematically in Fig 1 The arrangement of the electronic equipment is shown in the block diagram The output of the sound source (Permoflux, PDR-10) was transmitted to the external auditory meatus via an aural speculum (loosely filled with cotton) and a rigid plastic tube (length 35 mm, diameter 3 mm), along the central axis of which the sound probe connected to the measuring microphone (Bruel & Kjaer, type 4134) was situated with its tip 3 mm from the tympanic membrane The sound source emitting the carrier tone was fed by the output from the built-in tone generator of the wave analyzer (Radiometer type FRA 2T) The output from the probe microphone was measured with the wave analyzer

Experiments in animals

Further observations on the mechanism responsible for this type of impedance change were made in experiments performed on anaesthetized cats and guinea pigs

An increase in the intracranial pressure produced by transatlanto occipital injection of Ringer s solution consistently resulted in an impedance change, which started a few seconds after application of pressure and rose to a maximum after about 30 seconds After releasing the pressure it was often several minutes before full return of the impedance change to base line Bulging of the round window membrane as the pressure was raised indicated transmission of the hydrostatic pressure to the inner ear With increasing pressure the maximum response increased first almost linearly, and then asymptotically A response of 3–5 dB at the optimal frequency was usually attained at an intracranial pressure of 50 cm water The change affected the frequencies below 2 kc The magnitude and sign of the response varied with the frequency and with the animal species A characteristic curve from a cat experiment is shown in Fig 3 A An increase in the intracranial pressure produced by compression of the cervical veins in the same way as in the experiments on man resulted in an impedance change of the same type as that produced by intracranial injection of Ringer solution (Fig 3 B) Injection of this solution through a cannula inserted into the scala tympani of the basal turn produced a similar change in impedance (Fig 3 C)

Curarization or death of the animal did not influence the response This observation supports the assumption that the impedance change produced by an increase in intracranial pressure is a physical phenomenon and not mediated by, for example some unknown action of the middle ear muscles

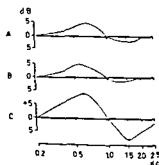


Fig 3 Frequency distribution and magnitude of the change in sound pressure at the tympanic membrane in response to transatlanto-occipital injection of Ringer solution (A) compression of the cervical vein (B) and injection of Ringer solution in the *scala tympani* (C) Recorded in the cat

RESULTS

Experiments in man

Observations were made in twelve normals where the presence of a normal middle ear function was confirmed by the sensitive stapedius muscle reflex test (Klockhoff, 1961)

When cranial stasis was established in the manner described above, a considerable impedance change was observed A representative record is shown in Fig 2 The impedance change appeared comparatively rapidly At a cuff pressure of 30 mm Hg it nearly attained maximum and remained fairly constant when the pressure was maintained at this level At the subsequent transient rise in cuff pressure to 50 mm Hg a smaller additional change in impedance was recorded, and a superimposed deflection pattern appeared which was found to be synchronous with the pulse of the subject Incidentally, the subject usually noted a clear attenuation of the carrier tone (550 cps) which presumably indicated a diminished transmission at this frequency.

In order to study the interaction on the impedance of increasing hydrostatic pressure and contractions of the stapedius muscle, stapedius reflexes were elicited from the contralateral ear with a tone at 10 dB suprathreshold intensity before, during and after compressing the cervical veins. As seen in Fig 2, the deflections due to the stapedial muscle contractions were reduced in amplitude during the initial phase of the pressure induced change in impedance, and disappeared at a higher level of stasis

The record in Fig 2 is representative of the normal subjects investigated with respect to the magnitude and type of the response In each individual the responses on each side were usually almost equal

To confirm the presumed anatomical origin of the impedance changes experiments were made on ten patients with otosclerotic fixation of the stapes In these cases little if any change in impedance was found The slight effect occasionally observed is not surprising, in view of the large variation in the extent and mechanical character of otosclerotic lesions



Fig 2 Representative acoustic impedance response recorded in a normal human ear in connection with a transient increase in the intracranial pressure produced by compression at the cervical vein the duration and the magnitude of the compression is indicated (in mm Hg) below the record The arrows indicate stimulation of the contralateral ear at a sound intensity of 10 dB above the threshold of the stapedius reflex

to such an extent as to mask minor changes in impedance at the stapedial footplate Nevertheless, the experimental conditions in the present investigation resemble those of Metz, and the results are in agreement with his

An increase in the cerebrospinal fluid pressure has been found to reduce cochlear microphonics (Hughson 1932, Krejci & Bornschein, 1951, Allen & Habibi 1962, Thalmann, Bornschein & Krejci, 1963) The effects appears to be due to several factors that are difficult to discriminate, namely interference with the inner ear circulation, which results in anoxia and various mechanical factors such as impaired sound transmission of the middle ear and deformation of the scala media The present experiments confirm the supposed effect of an increase in cerebrospinal fluid pressure on the middle ear mechanism but do not exclude the possibility of an additional effect on the organ of Corti, for instance a mechanism of a similar nature as the one which has been suggested to cause the typical low frequency loss seen in cases of Meniere's disease and possibly due to endolymphatic hypertension

On the anatomical and experimental evidence provided by the literature referred to in the introduction of this paper, the following pathways may be considered to be capable of transmitting hydrostatic pressure between the cranial cavity and the inner ear fluids

(1) *The cochlear aqueduct* connecting the perilymphatic space of the tympanic scale with the subarachnoid space (2) *The endolymphatic duct* connecting the endolymphatic system with the endolymphatic sac, which is enclosed between two split layers of the dura and situated on the infratentorial aspect of the temporal bone close to the sigmoid sinus (3) *The vascular bed of the inner ear* obtaining its arterial supply from the basilar artery and draining its venous blood into the inferior petrosal and the lateral sinuses (4) *The perineural spaces* of the nerves entering the labyrinth

The relative importance of these pathways to the pressure transmission is difficult to evaluate In all animals except primates the cochlear aqueduct has been considered to be the most important by virtue of its size In adult man the patency of this structure has been doubted (e g Karlefors 1924 Altmann & Waltner, 1950, Lempert *et al*, 1952) However, the pressure transmission must be associated with very small volume displacements since the inner ear fluids are enclosed within the rigid otic capsule, the only compliancy being provided by the round and oval windows For this reason even minute communications might contribute considerably to the pressure transmission

It is however likely that in man the cochlear aqueduct occasionally provides a rather wide communication with the cerebrospinal fluid space, since a large number of cases have been reported in which surgical opening of the perilymphatic space has *resulted* in a dramatic escape of liquid, the composition and volume of which indicate that it must be identical with cerebrospinal fluid This type of cases has been commented on by

Conclusion

An increase in the intracranial pressure is transmitted to the inner-ear fluids resulting in a change of the acoustic impedance of the middle ear

Clinical Observations

Having established the nature of the observed changes in impedance and found that they are normally present, bilaterally similar and easily reproduced with the employed technique, the possibility of applying the technique for diagnostic purposes was considered

The physiological and pathological significance of patent communications between the inner ear and the cerebro-spinal fluid is obscure In this connection it might, however, be pertinent to refer to the observations by Uyama (1933), who in some cases noted labyrinthine hydrops in rabbits after experimental obstruction of the cochlear aqueduct He suggested that the labyrinthine hydrops observed in Meniere's disease could be associated with a similar mechanism However, this hypothesis seems unlikely in view of the negative results of similar experiments conducted by Lindsay *et al* (1952) and Schuknecht & Kimura (1953)

Since the present method provides means of examining this problem in patients during the active stages of Meniere's disease, the technique was applied in five such cases The patients selected had normal middle ear function, they suffered from tinnitus, vertigo and had a unilateral fluctuating base deafness of perceptive type, which at the time of investigation was near the peak phase

In all 5 cases the provoked changes in impedance were found to be equal on the two sides and of the same magnitude and type as in the normal subjects It thus seems unlikely that there is any pathological restriction of the communication between cranial cavity and inner ear fluids in Meniere's disease

The method was also applied to one case of unilateral acoustic neurinoma, no significant influence on the response was observed

DISCUSSION

Previous investigations on the effect on sound transmission of an increase in the pressure exerted by the inner ear fluids as observed in experiments on fresh cadavre temporal bones, have given apparently conflicting evidence Using an acoustic impedance bridge connected to the external auditory canal, Metz (1946) found measurable impedance changes on applying hydrostatic pressure to the inner ear von Bekesy (1942), on the other hand, studied the difference in phase angle and volume *displacement* between sound applied to the drum and that appearing at the round window No effect was observed on applying a hydrostatic pressure In the former experiments the impedance change appeared over the impedance of the middle ear, whereas in *the latter this impedance was put in* series with that of the inner ear, thus possibly increasing the total impedance

to such an extent as to mask minor changes in impedance at the stapedial footplate Nevertheless the experimental conditions in the present investigation resemble those of Metz, and the results are in agreement with his

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several leading middle ear surgeons, for instance at the Second Workshop in Chicago on Reconstructive Middle Ear Surgery (1963). Klockhoff (1961) has reported a few cases in which there were spontaneous changes in impedance, manifested as slow, irregular, undulating waves with a superimposed pattern synchronous with the pulse and closely resembling the records obtained when the intracranial pressure is raised experimentally. This phenomenon suggests the presence of abnormally wide communications with the cranial cavity. Whether it has any pathologic significance remains uncertain.

The fact that the acoustic impedance of the ear is dependant not only on the individually different properties of normal middle ears but is also influenced by the intracranial and intralabyrinthine pressure might help to explain the difficulties encountered in demonstrating significant pathological values when *absolute* impedance measurement is applied for the diagnosis of middle ear disease. For such a purpose it seems to be more conclusive to elicit *relative* impedance changes as in the stapedius and tensor reflex tests (Klockhoff 1961) whereby individual differences of the absolute impedance do not interfere with the interpretation of the results.

In view of the limited material of the present investigation the observations presented in this paper must be regarded as preliminary, and although the first tentative clinical applications of the method have yielded negative results, it may well prove of value as a diagnostic aid in other aspects of the diversified field of labyrinthine and intracranial pathology.

RÉSUMÉ

L'investigation actuelle indique que chez l'homme comme chez certains animaux une augmentation de la pression intracranielle produite par la compression des veines cervicales a regulièrement pour resultat de considérables changements de l'impédance acoustique de l'oreille moyenne.

Des observations chez l'homme et des expériences sur les chats et les cobayes ont indiqués que ces changements de l'impédance sont produits par la transmission de la pression hydrostatique aux liquides labyrintiques qui par conséquent imposent à étrier une charge mécanique plus importante.

Des essais préliminaires de la méthode pour le but diagnostique dans cinq cas unilatéraux de la maladie de Ménière ainsi que dans un cas de neurinome du nerf acoustique furent negatifs, c'est à dire que les changements de l'impédance lors de l'augmentation de la pression intracranial furent bilateralement égaux et de la même grandeur que chez les sujets normaux.

Des possibilités anatomiques concernant la transmission craniolabyrintique de la pression hydrostatique ont été discutées et mises en rapport avec des cas de fuite excessive de liquides céphalo-rachidiens quelquefois observés dans la chirurgie de l'étrier et dans des cas particuliers de fluctuations spontanées de l'impédance acoustique de l'oreille moyenne. Le phenomène rapporté ci-dessus peut aussi partiellement expliquer les difficultés rencontrées en démonstrant les valeurs pathologiques significatives en employant des mesures absolues de l'impédance acoustique pour le diagnostique des maladies de l'oreille moyenne.

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HEARING AND NASAL FUNCTION CORRELATED TO POSTOPERATIVE SPEECH IN CLEFT PALATE PATIENTS WITH VELOPHARYNGOPLASTY

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82 patients with cleft palates and who had undergone velopharyngoplasty were examined one year after operation. The findings of aural pathology, hearing and nasal function were correlated to the postoperative speech evaluation. The incidence of aural pathology was 78 per cent. Despite the very high figure for aural pathology only 13 per cent of the patients had hearing losses of such a degree (30 dB or more) that it might influence the postoperative speech rehabilitation. Only 47.7 per cent of the patients had a good nasal function postoperatively. A correlation was found between the postoperative speech result regarding both hearing loss and nasal function, more marked for nasal function. Asymmetries in the nasal cavities were found to be responsible for postoperative asymmetries in the passages lateral to the velopharyngeal flap. It is evident that nasal function is just as important a factor as hearing for a good postoperative speech rehabilitation.

The surgical closure of cleft palate in early childhood results in a well functioning velopharyngeal muscular system and usually good speech. In adults with nonoperated cleft palates regular closure by the Veau-Wardill method has always resulted in velopharyngeal incompetence despite due retropositioning of the palate being obtained (Skoog 1965?). In such cases the functional results as regards speech are unsatisfactory. To overcome this the surgical procedure of a velopharyngeal flap has been performed on 82 patients operated on at the department of plastic surgery of the University Hospital in Uppsala. The surgical details have been presented by Skoog (1965?). This procedure was also described by Nylén in 1961 and will therefore not be repeated here. In the early part of th[illegible]

[illegible] way and the operative results is readily assessible for immediate and later inspection. In several cases the presence of an excessive amount of adenoid tissue in the nasopharynx made this an unsuitable donor site for flap operation. In other cases a larger flap was

required than could be obtained from the nasopharynx We were thus always able to elevate by direct approach through the mouth a pharyngeal flap based superiorly and of sufficient length and width to meet any demands in our series

From the oto-rhinological point of view hearing loss and impaired nasal function are the two main factors that besides the anatomical repair in itself may influence the postoperative speech in patients with cleft palates One special group comprises those patients in whom velopharyngoplasty has to be added to the usual Veau-Wardill closure The situation of these patients is obviously worse than in those who can be helped by operative repair alone

The aim of this investigation was to study the frequency of aural pathology and hearing loss and also the nasal function in a group such as this, consisting of highly selected severe cases Studies were made pre- and postoperatively and the results correlated to the pre- and post-operative speech evaluation performed separately by the phoniatrician of the Cleft Palate Team, Dr Hans Lindholm His observations will be published later, but the classification of the postoperative speech in these patients, given below, is taken from his report

MATERIAL

The material consists of 82 patients who, with regard to their preoperative conditions, may be classified as follows

Group 1 Patients with a nonoperated cleft palate at an adult stage With our present experience we are inclined to extend this group to comprise all patients above the age of five years

Group 2 Patients with incompetent palatopharyngeal function following cleft palate operations This group presented great anatomical and functional variations, from well united but short palates to scarred atrophic palates with reduced mobility, as well as varying degrees of soft palate tissue deficiency

In this latter group cinefluorography during connected speech (Skoog & Nylen, 1955, Bjork & Nylen, 1961) proved to be of great value in establishing an accurate diagnosis in some cases In patients with minor speech faults this technique made it possible to differentiate between those who were lacking the anatomical requirements for normal speech and would thus benefit from pharyngoplasty and where speech therapy alone would be of no or little value, and those who by speech therapy could be expected to make proper use of a dysfunctioning palatopharyngeal mechanism

58 patients had had previous cleft palate surgery and 24 had the velopharyngoplasty and surgical repair of the cleft palate in a one-stage procedure In 49 patients the pharyngeal flap was based superiorly, and in 33 patients inferiorly As however no correlation could be found between

TABLE 1 *Age at time of operation*

<10 years	10–20 years	21–40 years	>40 years	Total
8	22	33	19	82

the way in which the flap was taken and aural pathology, nasal function or speech results this factor is hereafter disregarded in this report For further details the reader is referred to Skoog's original paper

The age distribution within the group is of especial interest with regard to aural pathology and hearing As pointed out by Skolnik (1958) the incidence of aural pathology is only 6 per cent during the first year of life 27 per cent in pre-school children and 68 per cent in school children with cleft palates

METHODS

All patients had undergone a complete oto-rhinological examination microscopic examination of the drums and pure tone audiometry before the operation This was repeated at the follow up examination a year or more after the velopharyngoplasty At this follow up examination the nasal airway function was measured by a special method described in other articles (Aschan Drettner & Ronge 1956–1958) This method of simultaneous recording of the air flow through the nose and the pressure gradient between the oropharynx and the external nasal orifices was used by Drettner in 1960 on 63 patients with cleft palates preoperatively For further details the reader is referred to that report

RESULTS

Aural pathology

Out of 82 patients only 18 had bilaterally normal drums and another 6 patients had one normal drum The age distribution of these patients is the same as for the whole material Expressed differently, 122 ears out of a total of 164 showed marked pathological conditions including scars perforations collapsed drums etc Two ears had undergone radical operation in a further two antrotomy and in four patients tympanoplasty had been performed Despite the very high percentage of aural pathology only two ears out of 164 were suppurating at the follow up examination whereas 16 were not dry preoperatively In some of the patients with normal drums however the preoperative history showed middle ear infections which had healed with no after effects A total of 72 patients gave a positive answer when asked about middle ear infections

Hearing

49 patients out of 82 despite their aural pathology showed completely normal pure tone audiograms bilaterally and in a further 14 patients this

was normal for one ear. In only 10 patients did pure tone audiometry show bilateral hearing losses of 30 dB (*mean values of 500, 1000 and 2000 cps*) or more.

On comparing the hearing before and after velopharyngoplasty this was *found to be significantly better postoperatively* in 6 patients, the gain being 20 dB or more. This was mostly due to the fact that the ears had become dry.

The relationship between otoscopy findings and hearing was rather interesting. Out of the 42 ears with normal drums all but one showed normal hearing. In this ear there was complete perception deafness due to parotitis. 74 ears out of the 122 with marked aural pathology showed normal audiograms. Among the group of 48 ears with positive otoscopic findings and hearing loss only 20 ears—representing the 10 patients mentioned above—had a loss of 30 dB or more. The remaining 28 ears showed hearing losses that never exceeded 30 dB and in 14 of these the contralateral ears showed normal hearing.

Nasal function

Nasal malformation and the postoperative shape of the passage around the velopharyngeal flap provided some difficulties in measuring the nasal function in these patients. Objective measurements could only be performed in 44 patients. In an *additional 27 patients the nasal anatomy showed such* abnormalities and functional disorders that the patient was unable to perform nose breathing over a sufficient length of time for measurements to be made. In 13 patients, however, the obstruction was partly due to very narrow passages lateral to the velopharyngeal flap. In the remaining 11 patients the measurements could not be made for other reasons, these were mainly children who could not cooperate. The rhinological examination did, however, give some information about their nasal function, which was *classified as good* when no marked asymmetries were seen and the patient was able to breathe through both nostrils.

The material was divided into two main groups, with good and poor nasal function respectively. All the 27 patients who could not perform nose breathing were classified as having poor nasal function. A further 9 patients were added to this group, these including 7 in whom nasal function measurements were performed, the criterion here being that the values obtained lay outside the extreme values given by Drettner in 1960. The last two patients with poor nasal function were two of the 11 cases mentioned above and who could not breathe through the nose.

During the investigation marked asymmetries in the passages from oropharynx to nasopharynx lateral to the velopharyngeal flap were observed. 36 patients showed such marked asymmetries and during the investigation it became obvious that there was *some correlation between asymmetries in the nose and asymmetries in the postoperative shape of the passages around the velopharyngeal flap.* In 28 patients with one wide and

one narrow nasal cavity all showed a wide flap passage behind the wider and better functioning nasal cavity In those extremes where practically all nose breathing took place through one cavity anlone the opening behind was very wide, whereas the contralateral opening was often seen to be only a very narrow slit In the remaining 8 patients the nasal function and anatomy were very uncertain since, owing to septal defects and septal perfora tions among other things, no reliable evaluation could be made On the other hand, 7 patients with marked functional nasal cavity asymmetries showed symmetrical openings around the velopharyngeal flap

These findings indicate that the air currents passing through the nasal cavities must play an important role in forming the shape and size of postoperative passages around the sides of a pharyngeal flap

Speech Results Hearing and Nasal Function

From the phoniatrical *analyses of the postoperative speech* in *these* patients made by Dr Lindholm an overall evaluation gave the following results 22 had normal speech, 40 patients good speech and 20 poor speech Among the details included in this grouping intelligibility is, however, the most essential from the patient's point of view In 30 patients the intelligibility was found to be normal in 40 good and in only 12 poor

This material does not permit statistical analyses, but since the two opposite groups with normal and poor speech comprise practically the same number of patients the absolute figures for hearing and nasal function should give some idea of the role of these factors as regards speech results (cf Table 2) These figures, showing the high concentration of hearing losses and/or poor nasal function in the poor speech group, indicate that in many cases failure in giving the patient good or normal speech is probably partly due to these factors

Regarding the postoperative speech intelligibility a *similar analysis* of the whole material gives the *results* as shown in Table 3 From this table it is evident that the nasal function in particular influences the postoperative speech intelligibility whereas the role of the hearing loss is much less marked *in this respect*

Regarding open and closed nasalization no correlation between open

TABLE 2

Total number	Normal speech 22	Poor speech 20
Normal audiogram bilateral or unilateral	14 + 4	8 6
Hearing loss 30 dB or more bilaterally	1	6
Nasal function in number of patients good poor	16 6	8 12

was normal for one ear. In only 10 patients did pure tone audiometry show bilateral hearing losses of 30 dB (mean values of 500, 1000 and 2000 cps) or more.

On comparing the hearing before and after velopharyngoplasty this was found to be significantly better postoperatively in 6 patients, the gain being 20 dB or more This was mostly due to the fact that the ears had become dry

The relationship between otoscopy findings and hearing was rather interesting Out of the 42 ears with normal drums all but one showed normal hearing In this ear there was complete perception deafness due to parotitis 74 ears out of the 122 with marked aural pathology showed normal audiograms Among the group of 48 ears with positive otoscopic findings and hearing loss only 20 ears—representing the 10 patients mentioned above—had a loss of 30 dB or more The remaining 28 ears showed hearing losses that never exceeded 30 dB and in 14 of these the contralateral ears showed normal hearing

Nasal function

Nasal malformation and the postoperative shape of the passage around the velopharyngeal flap provided some difficulties in measuring the nasal function in these patients Objective measurements could only be performed in 44 patients In an additional 27 patients the nasal anatomy showed such abnormalities and functional disorders that the patient was unable to perform nose breathing over a sufficient length of time for measurements to be made In 13 patients, however, the obstruction was partly due to very narrow passages lateral to the velopharyngeal flap In the remaining 11 patients the measurements could not be made for other reasons, these were mainly children who could not cooperate The rhinological examination did, however, give some information about their nasal function, which was classified as good when no marked asymmetries were seen and the patient was able to breathe through both nostrils

The material was divided into two main groups, with good and poor nasal function respectively All the 27 patients who could not perform nose breathing were classified as having poor nasal function A further 9 patients were added to this group, these including 7 in whom nasal function measurements were performed, the criterion here being that the values obtained lay outside the extreme values given by Drettner in 1960 The last two patients with poor nasal function were two of the 11 cases mentioned above and who could not breathe through the nose

During the investigation marked asymmetries in the passages from oropharynx to nasopharynx lateral to the velopharyngeal flap were observed 36 patients showed such marked asymmetries and during the investigation it became obvious that there was *some correlation between asymmetries in the nose and asymmetries in the postoperative shape of the passages around the velopharyngeal flap* In 28 patients with one wide and

TABLE 4. *Hearing in ears with aural pathology*

	Normal	Mild loss	Moderate or severe loss
Skolnik 1958 (preoperatively)	11.1 %	65.2 %	33.7 %
This investigation (postoperatively)	60.0 %	23.4 %	16.6 %

with hearing loss in his extensive material, and Drettner (1960) found 49 per cent with hearing loss preoperatively in his material, partly including the same patients as in the present investigation. In view of these figures the 30 per cent found here in the whole material is surprisingly low and worth analysing. Skolnik's series of 401 patients investigated preoperatively is of especial interest. In Table 4 this author's figures for hearing loss in patients with aural pathology are compared with the corresponding but postoperative figures for the present investigation.

The differences are too large to be disregarded, but as Skolnik's figures are preoperative and the figures for this investigation postoperative, it can only be concluded that the anatomical repair of the soft palate protects the ears and partly restores the hearing. Drettner's (1960) figures point in the same direction.

On comparing pre- and post-operative audiograms in this investigation a significant hearing gain of 20 dB or more was observed in 6 patients and none showed reduced hearing. Four further patients had significantly improved hearing due to tympanoplasty and two as a result of antrotomy.

It appears evident that the disturbed tubal function in these patients is responsible for the aural pathology and that surgical reconstruction of the velopharyngeal anatomy in the form of velopharyngoplasty helps to restore the tubal function and thus the hearing. Compared with the high incidence of aural pathology the postoperative hearing losses in this material were surprisingly low, contrary to the figures anticipated. Skolnik's increasing figures for aural pathology with increasing age, i.e. 6 per cent for under 1 year, 27 per cent for 1–4 years and 34 [illegible] per cent for groups above 4 years, together with the figures given above concerning aural pathology and hearing, indicate that early reconstruction of the velopharyngeal anatomy will help to prevent hearing losses, thus facilitating the development of normal speech.

Nasal function

It is well known that the cleft palate, even postoperatively, may be combined with severe nasal deformities and disturbed nasal function. These conditions were pronounced in the present series. The objective method of nasal function measurement (Ivstam, Drettner & Bonge 1956–58) could

TABLE 3

Intelligibility	Number of patients	Normal and bilat + unilat	Hearing losses 30 dB or more bilat	Nasal function in number of pat good/poor
Very good	30	26	3	2/5
Good	40	28	4	16/24
Poor	12	9	3	1/8
Unintelligible	—	—	—	—

nasalization and nasal function was found. With closed nasalization measurements of the nasal function were only possible in 7 out of 27 patients, which might indicate a correlation, but this, however, could not be demonstrated in any other way.

Two patients had severe consonant faults but normal audiograms. In 29 patients with moderate consonant difficulties 14 had normal audiograms, 8 had moderate hearing loss and 7 marked high tone deafness.

DISCUSSION

Aural pathology and hearing

This group of patients who had to undergo velopharyngoplasty in addition to surgical repair of their cleft palates could be expected to show a higher incidence of aural pathology than cleft palate patients in general. Their tubal function must be more disturbed due, for example, to the abnormal anatomy of the velopharyngeal region and to the fact that the nasopharynx is more exposed to traumatization. Meissner (1939) found aural pathology in 82.8 per cent, Skolnik (1958) reported 45.8 per cent and Drettner (1960) 63 per cent. The corresponding figure in this investigation was 78 per cent, which actually represents the highest figure given in the literature during the last two decades. In view of improvements in therapy for *middle ear infections* and *in surgical methods* comparison should only be made with figures given for this period.

The age distribution within this group of patients shows that the majority of the patients were *over* 10 years of age. For patients of this age Skolnik's figure for aural pathology increases to 68 per cent. For the 74 patients above 10 years of age in this group the percentage of aural pathology increases to 82 per cent.

From the figures for aural pathology alone it may be concluded that these patients requiring velopharyngoplasty in addition to surgical repair of their cleft palates do in fact represent the highly selected, severe cases anticipated. It was also anticipated that the high incidence of aural pathology would influence the auditory and indirectly the speech results.

Halford & Ballenger (1956) found auditory impairment in 75 per cent and Whaley (1957) in only 25 per cent. Skolnik (1958) found 39.4 per cent

zeigte sich bei 78% der Fälle Trotzdem ergab sich nur bei 13% der Patienten ein solcher Hörverlust (30 dB oder mehr) der die postoperative Sprachen rehabilitation beeinflussen konnte Nur 17 7% der Patienten hatte gute nasale Funktion nach der Operation Zwischen den postoperativen Sprachergebnissen und den oto rhinologischen Befunden wurde hinsichtlich des Hörverlustes und der nasalen Funktion eine gegenseitige Abhängigkeit festgestellt, und besonders hinsichtlich der nasalen Funktion zeigte sich eine Aufeinanderbezogenheit Es wurde festgestellt dass Asymmetrien in den Nasenhöhlen postoperative Asymmetrien in den Passagen seitlich des velopharyngologischen Lappens verursachen Es ist offensichtlich dass sowohl die nasale Funktion als auch das Hörvermögen wichtige Faktoren für eine gute postoperative Sprachrehabilitation sind

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This group included 27 patients with such nasal deformities that they had no functional, open nasal airway. This figure is comparatively high compared to those of Drettner. Both groups were evaluated according to the same criteria Secondly the openings lateral to the velopharyngeal flap were so narrow that in 13 patients they interfered with the nasal function measurements

Tables 2 and 3 indicate that these observations regarding nasal function are of great interest when correlated to the postoperative speech The two groups with normal and poor speech may be compared directly, and the *number of patients with good/poor nasal function is 16/6 and 8/12* respectively. Regarding the intelligibility of the postoperative speech the same observation is made that good nasal function is essential for a good postoperative result Although the incidence of nasal cavity malformations in cleft palates has been noted in other studies (Skolnik, 1958; Lorenz, 1959, Drettner, 1960, among others), no figures like these demonstrating a correlation between these two conditions have been presented previously It seems evident that nasal function plays such an important role for the postoperative speech results that surgical restoration of the nasal cavities should also be taken into consideration in the rehabilitation of these patients

Practically all papers dealing with otological aspects of cleft palate patients stress the importance of good hearing for the speech result, see, for example, Skolnik (1958) and Drettner (1960) Tables 2–4 in this investigation also show the importance of hearing loss as a source of error in postoperative speech rehabilitation The figures given here for nasal function also show that poor nasal function is equally or even more detrimental to postoperative speech rehabilitation in cleft palate patients

This investigation gave an interesting and unexpected result Asymmetries in the passages lateral to the pharyngeal flap corresponded in 28 patients out of 36 to similar asymmetries in the function of the nasal cavities The explanation must be that a strong air flow helps to keep the passages free postoperatively, whereas the absence of air passing through results in narrowing of the passages This observation may be worth keeping in mind when interpreting the anatomical result of a pharyngeal flap operation

ZUSAMMENFASSUNG

82 Gaumenspalten Patienten mit einer Velum Pharynx Plastik wurden ein Jahr nach der Operation untersucht Besonderes Gewicht wurde auf die Ohrenpathologie sowie auf Gehor und Nasenfunktion gelegt wahrend der getrennt durchgefuhrten postoperativen Sprachenbewertung Eine Pathologie des Ohres

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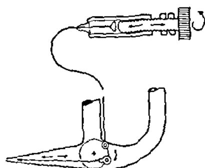
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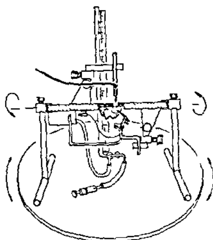


Fig 1 Fig 2

Fig 1 Stopcock for opening and closing the tip of the pipette by means of a camera cable release

Fig 2 Experimental arrangements on a turntable with the preparation connected to the APT system from the dorsal side and the electrodes for recording the vestibular activity from the ventral side The frog upside down

tip of the pipette which could be closed or opened during the experiments To avoid displacement of the pipette already introduced into the semicircular canal, the stopcock was governed by a camera cable release (Fig 1)

The electrical activity from the horizontal ampullar nerve was recorded using the same technique as Ledoux (1958) In a few preparations the isolated afferent activity was however, secured by cutting the proximal part of the nerve The integration of the activity over time was made in two parallel systems after amplification with aid of a Tektronix FM 172 (actual frequency range 80–1000 cps) and an audiomonitor (Grass AM 3, linear) The activity was then fed to a rectifying bridge (type Graetz) and parallel with it also to a decade counter and a rate meter previously used by us (Gleisner & Henriksson, 1964) The time constant for integrating pulses in the bridge was 0.86 sec The vertical bars in the figures indicating integrated activity amplitude were calibrated with regard to the voltage (mV) and frequency (imp min) respectively, leaving the two integrating systems Preparations were made (type A in the preceding paper) with the pipette introduced into the posterior vertical canal

After the pipette had been introduced into the posterior vertical canal from the dorsal side, the table was turned 180° around a horizontal axis and the electrodes applied to the horizontal ampullar nerve from the ventral side (Fig 2) The preparation was placed on a turntable which, by means of an electrical motor or by hand, could be given largely sinusoidal oscillations in the horizontal plane The angular velocity

VESTIBULAR ACTIVITY AT EXPERIMENTAL VARIATION OF LABYRINTHINE PRESSURE

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After proving elasticity within the walls of the membranous labyrinth in a previous paper, the same technique was now used for recording vestibular activity at different endolymphatic pressures. When the intralabyrinthine pressure was increased by instillation of fluid via the posterior vertical canal the activity in the horizontal ampullar nerve showed extensive variations lasting about as long as the saccule was changing its volume. After this change the activity resumed the level found at normal pressure. The rotatory responses at these positive pressures were largely the same as those found at the zero levels. At pressures below the zero level the rotatory response was nearly always abolished. Some membrane properties were discussed in relation to electrolyte ion concentrations in the perilymph. The findings were discussed in relation to the pathophysiology of Ménière's disease.

In a preceding paper (Henriksson, Gleisner & Johansson, 1966) a technique for varying the hydrostatic pressure within the labyrinthine endolymphatic space of the frog was described. As very little is known about the function of the ampullar organ at different endolymphatic pressures, the aim of this paper will be to describe experiments where this technique for application of pressure was combined with recordings of the activity from the vestibular nerve.

METHODS AND MATERIAL

The different hydrostatic pressures were applied to the labyrinth as described in the above-mentioned paper. It was found, however, that fluid in the system connecting the labyrinth with the air chamber – pressure transducer system (APT system) at rotation was forced out and into the labyrinth in pace with the rotatory oscillations used for stimulation. It was easy to prove that these movements of fluid were causing inadequate vestibular response. We therefore had to introduce a stopcock at the very

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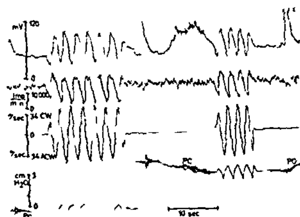


Fig. 4. Integrated nerve activity recordings and pressure level as in Fig. 3. Third tracing shows angular velocity (*ACW* anticlockwise, *CW* clockwise). *PC* indicates closing of stopcock in the pipette. Note the similarity between nerve activity responses at acceleration at different pressure levels.

IV. The rotatory vestibular responses did not change at increased endolymphatic pressure as compared to those at zero-level (Fig. 4). The similarity in the responses at the different pressures was quite apparent although a detailed analysis with respect to the relation in phase between stimulus and response has not yet been made. In all the rotatory experiments the rotations were preceded by a closing of the stopcock in the tip of the pipette.

V. When pressures below zero were present, there was always a considerable decrease in rotatory response; frequently this was even totally abolished. By raising the pressures the rotatory response could be restored (Fig. 5).

VI. In most preparations the vestibular activity decreased at repeated in-

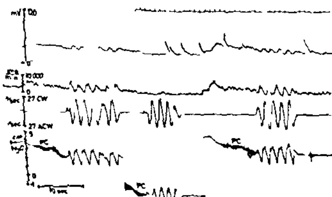


Fig. 5. Recordings as in *Fig. 4*. Note absence of rotatory response at negative pressure level.

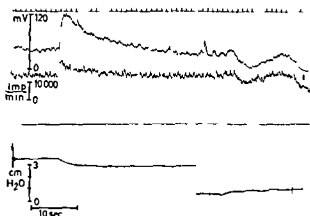


FIG. 3. Upper two tracing record integrated ampullar nerve activity and lower tracing record pressure variations at inflow and at outflow from the labyrinth. See also Fig. 1 in our previous paper (Henriksson, Gleisner & Johansson, 1965).

of the turntable was recorded by simple electrical means as previously described (Gleisner & Henriksson, 1964).

An inkwriter (Mingograf 81, Elema, Stockholm, Sweden) was used for recording of the different qualities studied—the integrated curves of vestibular activity, the angular velocity of the turntable, and the pressure.

The fluid used for instillation was in most experiments the previously described endolymphlike solution. In other experiments either distilled water, tap water or frog-Ringer was used. Sometimes these fluids were added with stains. For the experiments frogs (Rana temporaria) were used.

RESULTS

I. A pipette could be introduced into any semicircular canal with only a transitory change in activity in the ampullar nerve of the other canals.

II. When the APT system at an overpressure was connected to the labyrinth previously adjusted to the zero-level there was a change in the vestibular activity simultaneous with the rapid inflow to the labyrinth (Fig. 3). In most cases the activity showed a definite increase at instillation into the labyrinth. The duration of this change of activity could vary but very frequently the resting activity level was restored a few seconds after a stabilized pressure level was recorded.

When the labyrinth was allowed to force fluid out of itself, there was again a change of activity, though now in the reversed direction to that found at instillation. Thus an increase of activity at inflow was always followed by decrease at outflow or vice versa.

III. After the different positive pressures were reached the resting activity returned to the level present before instillation of fluid. The resting activity level at pressures below zero were very unpredictable but frequently fairly low activities were found.

the delimiting surfaces of cochlear endolymph cannot be penetrated by such stains

A permeability of Reissner's membrane for Na^{+} and K^{+} ions from the perilymph to the endolymph has been shown by using isotope technique but proofs of a reverse flow have not yet been found (Rauch *et al*, 1963) We did not find any significant rise of potassium concentration in the perilymph even after repeated periods of endolymphatic hypertension This possibly indicates selective ion flux properties in the walls of the endolymphatic system (with the reservation for dilution factors in the perilymphatic space)

The persistence of vestibular activity after instillation of Ringer's solution or water is in accordance with corresponding findings regarding microphonic potentials in the lateral canal organs of burbots (Flock, 1965).

Variations in the transitory reactions at inflow and outflow were also found when identical ionic concentrations were used This made an analysis of the effect of variation in ion-concentration on vestibular activity very difficult and although we believe that such an effect is probable, our findings do not admit of any conclusions of this kind

In experiments on living frogs with recordings from nerves with intact connection to the brain there were sometimes bursts of activity like those found in "efferent preparations" (Gleisner & Henriksson, 1964) The activity pattern in these preparations was otherwise not significantly different from those with only afferent activity Any clear-cut effect of the efferents on afferent activity could not be recognized

Although we are aware of the great difference between the frog's labyrinth and the human vestibular apparatus, there are also so many anatomical and physiological similarities that some discussion of human pathophysiology in relation to some of our findings may be attempted

Dilatations of the membranous labyrinth have often but not always been observed at operations on cases with Menière's disease In the same way as the frog's labyrinth the human labyrinth might possibly be able to regain its normal size after having acutely reached a dilated status The sudden and repeated attacks of vertigo in patients with Menière's disease may thus be regarded as occurring at rapid but transient dilatations of the endolymphatic space As to the mechanism for releasing the vertigo, deformations of the ampullas by the utricle as well as the pressure gradients in the semicircular canals causing cupular deviations might both be responsible

As mentioned earlier (in the preceding paper) ruptures of the membranes have also been *considered* to be responsible for the vertiginous attacks Under such conditions the elasticity of the membranes might force endolymph into the *perilymphatic* space and also contribute to the collapsing of parts of the membranous *labyrinth*

The normal rotatory response from the horizontal ampulla during even [illegible] ures might also be discussed *in relation*

stillations Some preparations showed, however, very good nervous response in spite of repeated instillations We did not find any consistent relation between vestibular activity and different kinds of fluids used for instillation Even regular tap water was used for instillation without abolishing the activity.

DISCUSSION AND CONCLUSION

Here will be discussed the findings in the preceding and the present papers Our studies accounted for in these two papers have been restricted to hydrostatic pressure variations while osmotic factors have not been controlled

A bulging of the "perilymphatic" membranous walls before they were penetrated indicates a positive physiological pressure On account of the thin walls in the membranous labyrinth this pressure might be assumed to exist also in the endolymphatic space The flattening of the saccule after removal of some of the perilymph might, however, indicate that the pressure within the endolymphatic space is not essentially higher than that of the perilymph In the same direction might be interpreted the fact that the saccule did not further collapse and that little if any fluid could be seen leaving the semicircular canal when this canal was cut on the upper side of the preparation

The relation between the amount of fluid added to the labyrinth and the resulting pressure within it indicates an elasticity within the membranes which makes it possible for the labyrinth to—as far as could be judged from the microscopic observation—regain its original volume after distension It must also be pointed out that the labyrinth could be distended repeatedly without much loss of elasticity These elastic properties of the labyrinthine membranes have up till now not been studied but might furnish essential data for our understanding of the labyrinthine physiology

From the experiments could also be derived some information about the mechanism for restoring the normal pressure within the labyrinth after application of high pressures Although in some experiments we could establish a patency of the endolymphatic duct this did not seem to be the only pressure-regulating factor Thus no significant difference in decrease of pressure could be recorded whether the endolymphatic sac was opened or not or whether the duct was blocked or not The role of the vessels in the regulating mechanism may be indicated by the fact that they became stained by the dye sometimes added to the fluid used for instillations A loss of fluid from the labyrinth may also take place through the membranes but this could not be proved by the experiments

Our experiments showed, however, that in spite of repeated instillations membranes of the labyrinth are capable of preventing stains from passing from the endolymph to the perilymph, at least in visible amounts This is in accordance with the findings by Tonndorf, Duvall & Reneau (1962) that

ERYTHROBLASTOSIS FOETALIS AND THE HEARING ORGAN

A Pathological Study

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After a brief review of clinical and pathological studies of the influence of erythroblastosis foetalis upon the hearing organ, the authors report the case histories and pathological findings in 4 newborn infants with various types of blood group immunization and of one patient with hyperbilirubinaemia following liver damage. The temporal bone findings did not differ definitely from those demonstrated in similar patients without haemolytic disease of the newborn. The auditory nuclei showed perivascular haemorrhages and scattered ganglion cell degenerations, but these changes were equally common in neighbouring nuclear areas in the basal parts of the brain and in the brain stem. The short lifetime was a probable explanation why yellow pigmentation was not demonstrated in the central nervous system of the 4 sensitized patients. The pathological findings afforded no possibility of distinguishing between the influence of erythroblastosis and of birth damage upon the organ of hearing. In our opinion the effect of erythroblastosis upon the hearing organ is due rather to the anaemic anoxic insult than to a toxic action by the bilirubin itself.

Since Goquet in 1944 reported on an infant with icterus neonatorum, rigidity of the lower limbs and impaired hearing, numerous papers on the relationship between erythroblastosis foetalis and hearing loss of early onset have been published. Nevertheless, a number of clinical and pathological aspects of this subject have not yet been sufficiently elucidated.

Haemolytic diseases of the newborn may be due to Rhesus incompatibility, sensitization to some Rhesus sub-groups, or immunization in the ABO system. So far, vaccination has been a fairly unheeded cause and is presumably of most importance as a causative factor in the early part of pregnancy.

Erythroblastosis foetalis occurs in about $1/2$ per cent of all newborns. The syndrome has been described by Gerrard (1952). The mortality and the incidence of neurological symptoms among the survivors have been appreciably reduced after the introduction of exchange transfusion (Cavanagh 1954).

The pathological diagnosis, kernicterus, is now used in an extended

to Menière's disease In early cases of this disease the caloric response is frequently also normal indicating that the condition of the diseased labyrinth can be compatible with normal function of ampullar organs

ACKNOWLEDGMENT

We gratefully acknowledge the help of Mr Alf Lundberg in designing the glass pipette, its stopcock and glass connections

ZUSAMMENFASSUNG

In einer früheren Arbeit wurde die Elastizität innerhalb der Wände des membranösen Labyrinths nachgewiesen In der vorliegenden Arbeit wird die gleiche Technik zur Aufzeichnung vestibulärer Aktivität bei verschiedenem endolymphatischem Druck angewandt

Nachdem der intralabyrinthäre Druck durch Instillation von Flüssigkeit in dem hinteren vertikalen Bogengang erhöht worden war konnte im horizontalen Bogengangsnerv eine grosse Aktivitätsveränderung registriert werden und zwar so lang wie die Veränderung des Sacculusvolumens anhielt Danach wurde die normale Aktivität wieder registriert Die durch diesen positiven Druck hervorgerufenen rotatorischen Aktivitäten waren weitgehend die gleichen wie diejenigen, die bei Normaldruck gefunden wurden Unterhalb des atmosphärischen Drucks wurde die rotatorisch hervorgerufene Aktivität beinahe immer gehemmt Einige Membraneigenschaften wurden in Beziehung auf die Zusammensetzung der Elektrolyten in der Perilymphe diskutiert Die Beziehungen der Resultate zur Pathophysiologie der Menièreschen Krankheit wurden besprochen

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	No. of children examined	Erythroblastosis %	Birth injuries %	Prematurity %	Aetiology not elucidated %
Bordley & Hardy 1951	296	4	8		35
Bordley 1952	485	6	3		29
Kinney 1953	630	2	4		
Arnvig 1954	484	1	8	2	22
Fowler & Basek 1954	270	5	8		
Johnsen 1954	111	5	10	10	32
Sorensen 1958	140	6	7	23	20
Zonderman 1959	328	7	9	6	45
Fraser 1964	1509	4	2	2	0

palsy. Presumably only a small proportion of these palsies is due to erythroblastosis foetalis but most clinicians, like many neuropathologists, incline to a central genesis of the hearing impairment in this disease (Barr & Wickhoff 1959, Terkildsen 1960, Fisch & Osborn 1954, Dublin 1951).

Barnett & Ryder (1950) stated that even a severe erythroblastosis need not necessarily involve brain damage. They add that hearing impairment in such cases may be of peripheral origin.

Crabtree & Gerrard were the first to report the results of pathological studies of the temporal bones and brain stem from a patient with kernicterus. They found no definite changes in the peripheral hearing organ, but highly disintegrated ganglion cells in the dorsal and ventral cochlear nuclei.

In another study of 2 infants who had died of erythroblastosis and kernicterus during the neonatal period Gerrard found only cellular degenerations in the dorsal and ventral cochlear nuclei.

Goodhill (1956) has mentioned that Wolff & Goodhill in an unpublished study had found certain cellular degenerations in the spiral ganglion of a patient with kernicterus. However, these changes were interpreted as being secondary to central damage.

In 1956 Kelemen reported the study of the temporal bone from a full term girl who had died of erythroblastosis on the 3rd day of life despite exchange transfusion. In the inner ear the sensory organs and nerve ganglia were intact, while the walls of the membranous labyrinth were displaced on both sides. The vestibular scala and the perilymphatic cisterna were dilated. So was the endolymphatic sac. The rugae of the latter structure were highly oedematous. Kelemen did not feel that he could draw definite conclusions from these findings, but he emphasized, like Gerrard before him, the necessity for further pathological studies of the perceptive organ from patients with erythroblastosis foetalis.

Present Investigations

In a series of 135 temporal bones from 73 newborn infants there were 2 instances of Rhesus immunization, one of A sensitization and one of B

sense to apply to the neurological abnormalities caused by the damage to the basal parts of the brain.

Kernicterus is not pathognomonic of haemolytic disease of the newborn and nowadays it occurs in less than 15 per cent of infants with Rhesus immunization. Similar syndromes have been reported after haematogenous sepsis, hepatitis, toxic liver damage, atresia of the bile ducts, and hypoglycaemia.

Gerrard assumed that kernicterus was caused by an unknown factor whose effect was intensified in infants with Rhesus sensitization. Moreover, hypoxia may be imagined to compromise those enzymes which normally conjugate bilirubin. Indeed, several authors have pointed out birth asphyxia as a likely cause of the lesion (Dublin, 1951).

Most recently, it has been proved possible to induce kernicterus in monkeys and in rabbits by combining administration of bilirubin to the newborn animals with provoked asphyxia (Windle, 1963, Chen *et al.* 1965).

Prematurity has been mentioned as an important predisposing factor by Aidin *et al.* (1950). Gerrard found that 18.3 per cent of the patients who were hard of hearing in his series were premature, while the incidence in the general population was 6.9 per cent. Incidentally, 35 per cent of his patients with icterus neonatorum were premature.

Goodhill (1947) reported that even sub-clinical erythroblastosis may be imagined to affect hearing. The reported incidence of hearing loss following kernicterus is extremely varied.

Goodhill (1950) found a striking similarity of the audiometric curves from a number of patients with kernicterus, birth injuries, and cerebral palsy. He believed that the injury might affect any part of the perceptive organ. Like a few previous authors Crabtree & Gerrard (1950) found the dorsal and ventral cochlear nuclei to be involved in the damage caused by kernicterus. The following tabulation lists the percentage of hearing impairment which the various authors have attributed to erythroblastosis, birth injuries and prematurity.

Owing to different principles of classification and differences in the case materials it is difficult to correlate the various analyses. However, erythroblastosis does not appear to predominate particularly in any special series. The low frequence in Arnvig's series may be due to the fact that serological study was not practicable in all cases where it might have been desirable. Retrospective analyses of this nature involve uncertainties in respect to diagnosis as well as history. Hearing impairment in the wake of kernicterus often co-exists with other neurological abnormalities and in such instances the assessment is often very difficult. In this connection it has been emphasized by Cohen (1956) that aphasoid syndromes are easy to mistake for hearing impairment in these cases.

Most recruitment studies on patients with hearing impairment of early onset have been concerned with young individuals having athetoid cerebral

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vascularis was atrophic, while the organ of Corti as well as the membranous and neural structures of the vestibular part showed no definite changes

In the left temporal bone there was a fairly large haemorrhage in the inner acoustic meatus In several preparations the organ of Corti was rather narrow, but the changes were not present throughout the serial sections and were presumably due to artefacts The remaining structures of the temporal bone did not differ from the findings on the right

Case 2

About 2 months before term a live, primarily asphyctic girl weighing 1500 g was born in the left occipito anterior presentation Her mother had previously been delivered of one normal infant and two prematures both of whom had died of Rhesus sensitization In the present pregnancy the Rhesus antibody titre had been constantly elevated (indirect Coombs test 32, 16, 32 16) The infant weighed 1500 g was pale and had insufficient respiration, but did not exhibit jaundice, oedema, or visceral enlargement Her blood group was 0, Rhesus positive, and the erythrocytes showed moderate to severe sensitization *Haemoglobin* 68 per cent, reticulocytes 70 per thousand, serum bilirubin 4 3 mg/100 ml After exchange transfusion a few hours after birth the haemoglobin level rose to 109 per cent, and the bilirubin fell to 3 0 mg/100 ml In spite of active measures the infant went rapidly downhill in the course of the next 24 hours The bilirubin content increased to 17 7 mg/100 ml, and death ensued after about 36 hours of life

The post mortem diagnoses were prematurity, subtotal pulmonary atelectasis, subarachnoid haemorrhage

There was no yellow pigmentation of the skin, viscera or brain No enlargement of the liver or spleen The cranial bones and pachymeninges showed no signs of injury The leptomeninges were oedematous, showing distinct vascular congestion Over both hemispheres there were widespread subarachnoid haemor rhages Blood clots were present in both posterior horns and heamatomas around the terminal veins on the right The basal ganglia did not show pigmenta tion

Microscopic examination revealed no ganglion cell degeneration in the cortex Some astrocytic reaction in the centrum ovale The basal ganglia showed scattered perivascular haemorrhages in the germinative tissue, but these structures too showed no definite degeneration of the ganglion cells The brain stem showed a number of small haemorrhages Especially in the vestibular nucleus, dorsal and ventral cochlear nuclei and substantia nigra there were definite, though not particularly severe, changes of the ganglion cells

The right temporal bone showed an even more ample tympanic mesenchyme with some congestion, but no bleeding or infection The free cavity contained only small quantities of amniotic debris The stapedial artery was still present The internal acoustic meatus contained moderately severe extravasates of blood The modiolus showed no definite changes, and the cavities of the cochlea no accumulations of blood Minor extravasatees of blood in the vestibule were persumably due to artefacts as the saccule had ruptured In this temporal bone too the stria vascularis looked atrophic, while the cochlear as well as vestibular sensory organs were intact as were the nerve ganglia

sensitization Moreover, there was one case of hyperbilirubinaemia which was probably due to neonatal hepatitis

In the present study the pathological findings in the brain and temporal bones were correlated with the data in the obstetrical records for the purpose of investigating the site and nature of the damage as well as the significance of the bilirubin level and anoxia to the damage.

CASE REPORTS AND FINDINGS

Case 1

A boy weighing 3400 g with primary asphyxia was born at term in his home His mother had a history of 4 pregnancies, but only the first one had terminated in the delivery of a live infant. In this, her fifth pregnancy, there had been a highly elevated Rhesus antibody titre in her blood (indirect Coombs test 256) A couple of hours after birth the infant was admitted to the Paediatric Department of the University Hospital in an extremely debilitated state His blood group was A, Rhesus positive, haemoglobin level 22 per cent, reticulocyte count 175 per thousand, bilirubin 4 7 mg/100 ml There was unmistakable hepatomegaly and fairly extensive oedema The red cells were moderately to severely sensitized At exchange transfusion, about 5 hours after birth, the haemoglobin level rose to 130 per cent, and the serum bilirubin fell to 3 0 mg/100 ml However, the condition soon deteriorated again, and in spite of active ventilation the baby died about 20 hours after birth

Autopsy showed Erythroblastosis foetalis, rupture of the spleen, subtotal pulmonary atelectasis, subgaleal and subarachnoid haemorrhage, as well as perivascular haemorrhage in the brain

There was not a definitely yellow pigmentation of the skin, viscera, or brain The liver was definitely enlarged, weighing 220 g (normal weight 160 g) Cutting of the brain after a few days' fixation did not show any bile pigment in the characteristic kernicterus sites Extravasated blood was found in the cisterna pontis, around the cerebellum, and in the white matter of the brain dorsal to the lateral ventricles

Microscopic examination revealed perivascular bleeding in the leptomeninges, centrum ovale, basal ganglia, and brain stem Degeneration of ganglion cells was found, mild in all cell groups of the basal ganglia, more severe in the globus pallidus Furthermore, there was slight ganglion cell degeneration in all the cranial-nerve nuclei The changes were most massive in the hypoglossal nucleus, less marked in the dorsal and ventral cochlear nuclei

In the right temporal bone the middle ear was covered with a fairly narrow rim of connective tissue showing vascular congestion, but no major haemorrhage In the free cavity there were colonies of amniotic debris erythrocytes, and lymphocytes In the internal acoustic meatus there were moderate perineural extravasates of blood The vessels of the modiolus exhibited congestive phenomena, and while the spiral ganglion was normal, the cells of the vestibular ganglion showed incipient nuclear changes No extravasated blood was present in the cochlea Several preparations showed Reissner's membrane to be ruptured in the basal turns, but in a normal position in the other two turns The stria

In the left temporal bone there was a large extravasate of blood in the basal part of the scala tympani As on the right, these sections showed mild autolytic changes

Case 4

Four years previously her mother had given birth to an infant affected with neonatal jaundice erythroblastosis foetalis but not anaemia This child had died at the age of 3 years from brain damage sustained by B sensitization During the present pregnancy the mother had exhibited immune antibody B of moderately high to high titre She was admitted to Obstetrical Department A of the University Hospital for drug induction of labour as the foetus was estimated to weigh roughly 2500 g As labour could not be induced Caesarean section was performed about 2 weeks before estimated term A primarily asphyctic girl of 2400 g was delivered She was in the cephalic presentation and the cord was wound twice around her neck Her blood group was B Rhesus positive haemoglobin level 62 per cent and serum bilirubin 18 3 mg 100 ml No reticulocytes were demonstrated in the blood The direct Coombs test was negative The Munk Andersen test was strongly positive

Three hours after birth the girl was given an exchange transfusion with fresh donor blood group 0 to which was added B substance The haemoglobin level rose to 130 per cent while the serum bilirubin fell to 2 6 mg/100 ml Thereafter the infant rallied but soon had further attacks of cyanosis and respiratory embarrassment and died in spite of positive pressure ventilation after having lived for 18 hours

The post mortem diagnoses were subtotal pulmonary atelectasis pericardial petechiae

No jaundice of the skin viscera or brain tissue The examination also did not disclose enlargement of the viscera or generalized oedema The cranial bones and pachymeninges were intact In the leptomeninges there was moderate oedema and more severe congestion Cutting of the cerebrum showed no signs of kernicterus Microscopic examination revealed the cortical ganglion cells to be without any signs of degeneration In the centrum ovale there were severe hyperaemia some astrocytic reaction and a few necrotic foci The basal ganglia showed a number of lipid containing macrophages as well as shrunken ganglion cells laterally in the thalamus and globus pallidus while the subthalamic nucleus was without degenerations.

In the brain stem severe hyperaemia was present in several sites Scattered cellular degenerations occurred in the hypoglossus nucleus oliva vestibular nuclei and in the dorsal as well as ventral cochlear nuclei

In the right temporal bone there was only a small quantity of loose fibrillar connective tissue with numerous vacuoles and some vascular congestion The free cavity contained a number of squamous cells In the internal acoustic meatus there were several congestive phenomena but only little bleeding The nerve ganglia did not exhibit definite changes and the cochlear cavity showed no haemorrhages In many sections Reissner's membrane was tied down to the flattened organ of Corti and the stria vascularis was of an atrophic appearance No definite abnormalities were demonstrated in the saccule utricle or the other membranous or neural structures

In the left temporal bone there was also ample residual foetal tissue in the middle ear cavity Like the internal acoustic meatus the scala tympani contained fairly ample quantities of extravasated blood As on the right the stria vascularis was slightly atrophic There was slight disintegration of the organ of Corti The spiral and vestibular ganglia were intact

Case 3

Two months before term a youngish woman was *delivered of her first infant* in a municipal lying in department The infant a boy weighing 1350 g presented by the breech He was slightly asphyctic and had a right sided Duchenne Erb paralysis as well as facial palsy He was transferred to a department for prematures where his condition deteriorated through the next days He developed jaundice and had several short lasting seizures His haemoglobin level was 120 per cent reticulocyte count 40 per thousand Serum bilirubin 11 7 mg 100 ml Blood group A Rhesus positive Direct Coombs test negative The Munk Andersen test was questionably positive The maternal blood group was 0 Rhesus positive, and the serum contained α haemolysin The anti A titre was definitely elevated so that A sensitization was definitely established

As the bilirubin content increased *during the next 24 hours to 23 4 mg/* 100 ml the patient was transferred to the Paediatric Department of the University Hospital After an exchange transfusion with fresh donor blood group 0 Rhesus positive to which was added A substance the boy rallied somewhat but was still pale and jaundiced His haemoglobin level and bilirubin content remained approximately unchanged but the patient died rather suddenly at the age of 15 days

The post mortem diagnoses were prematurity congenital heart disease atresia of the pulmonary artery deficiency of the interventricular septum patent foramen ovale patent ductus arteriosus almost total pulmonary atelectases infratentorial subarachnoid haemorrhage

Gross inspection showed no enlargement of the viscera oedema or *jaundice* of the skin Neither the viscera nor the brain showed yellowish pigmentations The cranial bones were intact Possibly the tentorium cerebelli had ruptured Fairly extensive subarachnoid haemorrhages were spread plaque shaped over the cerebellar hemispheres A cut through the unfixed brain showed no yellow pigmentation of the basal ganglia or medulla oblongata Microscopic examination of the central nervous system had not been performed

In the right middle ear there was ample vascular congestion and a number of small perivascular haemorrhages in the rather narrow rims of connective tissue Clusters of squamous cells and of red and white blood cells characterized the free cavity In the internal acoustic meatus as well as in the modiolus there was pronounced *congestion and a few haemorrhages Major and minor accu*mulations of erythrocytes were forcing their way into the spiral ganglion and scala tympani In the scala vestibuli too there were extravasates almost totally filling the helicotrema The scala media was uninvolved On the other hand there was pronounced perilymphatic haemorrhage around the ampulla of the lateral semicircular canal The cupula was partially destroyed Serofibrinous deposits were seen in the vestibular as well as cochlear parts Mild autolytic changes affected the stria vascularis as well as the organ of Corti The same applied to the sensory organs in the vestibular parts

In the left temporal bone there was a large extravasate of blood in the basal part of the scala tympani. As on the right, these sections showed mild autolytic changes.

Case 4

Four years previously, her mother had given birth to an infant affected with neonatal jaundice, erythroblastosis foetalis, but not anaemia. This child had died at the age of 3 years from brain damage sustained by B sensitization. During the present pregnancy the mother had exhibited immune antibody B of moderately high to high titre. She was admitted to Obstetrical Department A of the University Hospital for drug induction of labour, as the foetus was estimated to weigh roughly 2500 g. As labour could not be induced, Caesarean section was performed about 2 weeks before estimated term. A primarily asphyctic girl of 2700 g was delivered. She was in the cephalic presentation, and the cord was wound twice around her neck. Her blood group was B, Rhenus positive, haemoglobin level 62 per cent, and serum bilirubin 18.3 mg/100 ml. No reticulocytes were demonstrated in the blood. The direct Coombs test was negative. The Munk Andersen test was strongly positive.

Three hours after birth the girl was given an exchange transfusion with fresh donor blood group 0 to which was added B substance. The haemoglobin level rose to 130 per cent, while the serum bilirubin fell to 2.6 mg/100 ml. Thereafter, the infant rallied, but soon had further attacks of cyanosis and respiratory embarrassment and died, in spite of positive pressure ventilation, after having lived for 18 hours.

The post mortem diagnoses were: subtotal pulmonary atelectasis, pericardial petechiae.

No jaundice of the skin, viscera or brain tissue. The examination also did not disclose enlargement of the viscera or generalized oedema. The cranial bones and pachymeninges were intact. In the leptomeninges there was moderate oedema and more severe congestion. Cutting of the cerebrum showed no signs of kernicterus. Microscopic examination revealed the cortical ganglion cells to be without any signs of degeneration. In the centrum ovale there were severe hyperaemia, some astrocytic reaction, and a few necrotic foci. The basal ganglia showed a number of lipid containing macrophages as well as shrunken ganglion cells laterally in the thalamus and globus pallidus, while the subthalamic nucleus was without degenerations.

In the brain stem severe hyperaemia was present in several sites. Scattered cellular degenerations occurred in the hypoglossus nucleus, oliva, vestibular nuclei and in the dorsal as well as ventral cochlear nuclei.

In the right temporal bone there was only a small quantity of loose fibrillar connective tissue with numerous vacuoles and some vascular congestion. The free cavity contained a number of squamous cells. In the internal acoustic meatus there were several congestive phenomena but only little bleeding. The nerve ganglia did not exhibit definite changes, and the cochlear cavity showed no haemorrhages. In many sections Reissner's membrane was tied down to the flattened organ of Corti and the stria vascularis was of an atrophic appearance. No definite abnormalities were demonstrated in the saccule, utricle, or the other membranous or neural structures.

In the left temporal bone the organ of Corti was less flattened than in the right. Apart from mild cadaverous changes especially in the vestibular sensory organs the appearances were normal.

Case 5

A youngish woman was delivered of her first baby in her home 8-10 weeks before term. Owing to primary asphyxia the premature boy was immediately admitted to the Paediatric Department of the Copenhagen County Hospital in Gentofte. His birth weight was 1400 g. Haemoglobin level 125 per cent, serum bilirubin 28.1 mg/100 ml, prothrombin 28 per cent, blood group 0 Rhesus positive. Owing to increasing bilirubin values the infant was transferred to the Paediatric Department of the University Hospital. Up till that time he had been treated in an incubator.

The maternal blood group was 0, Rhesus positive. No immune antibodies had been demonstrated. There was direct compatibility between the maternal serum and the infant's blood cells. In spite of active treatment, the boy's condition deteriorated in the cource of the next days and he died on the 5th day after birth.

The post mortem diagnoses were: prematurity, severe jaundice of the skin and viscera, scattered necroses in the liver, subtotal pulmonary atelectasis with alveolar haemorrhages, slight scattered haemorrhage in the subarachnoid space and perivascularly in the brain.

The liver weighed 55 g and thus was not enlarged. Microscopic examination revealed widespread and confluent necroses in the parenchyma. These lesions appeared to be recent and the outlines of the liver cells could be discerned while the nuclear pattern was obliterated. There was some desposition of fibrin, granulocytic infiltration and mild biliary stasis. No atresia of the biliary ducts and no giant cells. Only sparse haematopoietic tissue. The most likely diagnosis was neonatal hepatitis.

There were no signs of cranial injuries. The tentorium and falx were intact and the subarachnoid haemorrhages were most marked in the posterior fossa as well as in the temporal regions. The leptomeninges showed a faint yellow pigmentation but in the cerebrum there were no signs of Icterus on cutting after a few days fixation.

Microscopic examination revealed perivascular haemorrhages in the leptomeninges and a small haematoma around a terminal vein. No degeneration of ganglion cells in the cortex of the cerebrum or cerebellum, basal ganglia or brain stem. No definite signs of degeneration in the vestibular nucleus or in the dorsal and ventral cochlear nuclei.

In the right temporal bone it was impossible to assess the appearances of the middle ear satisfactorily because of artefacts. The inner acoustic meatus showed ample perineural extravasates of blood. The modiolus showed vascular congestion but the spiral ganglion like the vestibular ganglion did not exhibit definite changes. There was slight disintegration of the stria vascularis. Rather severe serofibrinous deposits characterized the peri- and endolymphatic parts of the labyrinth. The organ of Corti and the vestibular sensory epithelia showed no characteristic changes.

In the left temporal bone there was ample foetal mesenchyme in the tympanic cavity. There were quite a number of vacuoles and severe vascular congestion,

but no major haemorrhages The free cavity contained some amniotic debris and clusters of lymphocytes The connective tissue rim showed no inflammatory infiltrations The findings in the labyrinth did not differ fundamentally from those on the right

The widespread hepatic necroses could account for the hyperbilirubinaemia The maternal blood was investigated for toxoplasmosis but the serological reactions did not adduce any evidence to support this diagnosis As the vascular changes found in the infant could not explain the hepatic necroses and as inclusion bodies were not discovered anywhere infection had to be considered the most likely aetiological cause

COMMENTS

Pathological studies of 4 patients with serologically confirmed immunization and one with hyperbilirubinaemia following liver damage showed definite jaundice of the skin and viscera only in the last mentioned one None of the patients showed the characteristic yellow pigmentation of those parts of the brain which are usually involved by kernicterus However the patients had lived for only 20 hours 36 hours 15 days 18 hours and 5 days respectively

Case 1 had definite hepatomegaly severe anaemia and an elevated reticulocyte count Cases 2 and 4 also had anaemia and an increased reticulocyte count but no oedema or visceral enlargement During their short lifetimes none of the sensitized patients reached such high serum bilirubin values as Case 5

The pathological findings in the central nervous system consisted mainly in perivascular haemorrhages and ganglion cell degenerations Only Case 4 did not exhibit subarachnoid haemorrhage on brain autopsy The degenerative changes of the ganglion cells and central pathways were present chiefly in the basal ganglia and medulla oblongata but did not differ from the lesions which are caused exclusively by anoxia The damage had not affected the cortical areas or the spinal cord The vestibular as well as the acoustic nuclei were often involved but the dorsal and ventral cochlear nuclei probably not more so than the other nuclear structures in the area

As might be expected the investigations of the temporal bones showed the middle ear content of foetal connective tissue to depend among other things upon the developmental stage of the foetus Vascular congestion and haemorrhage were of the same degree and frequency as in similar patients without erythroblastosis

All 5 patients had major or minor perineural extravasates of blood in the inner acoustic meatus Haemorrhages in the scala tympani were present in Cases 2 and 3 and the latter also had blood in the scala vestibuli spiral ganglion and the lateral ampulla of the semicircular canal on the right Case 1 had mild degenerative changes in the vestibular ganglion Since autolytic changes did not otherwise characterize this series of temporal bones and since the spiral ganglion was entirely intact this finding

might perhaps be of a specific genesis. However, as ganglion cell degenerations did not occur in other temporal bones of this series, we did not regard the finding as of definite pathological significance.

The organ of Corti was flattened in several sites in Cases 1 and 4. However, this was an inconstant finding and heterogeneous in the two temporal bones from the same patient, so that no definite importance could be attached to this either.

In Cases 1, 2, and 4 the stria vascularis was of an atrophic appearance. Similar findings were demonstrated in a number of newborn infants with a history of asphyxia, and anoxic vascular damage may also be suspected in these cases.

The presence of severe pulmonary atelectases in all 5 patients emphasizes the likelihood of an asphyctic cause of the confirmed injuries to the central nervous system and temporal bones. While Case 1 had marked primary asphyxia and a haemoglobin level of 22 per cent, the massive temporal bone haemorrhages and the presence of facial palsy as well as seizures in Case 3 were more reasonably related to the difficult breech delivery. In this as well as in other similar cases, however, it was impossible to distinguish the influence of the traumatic from that of the anoxic insults.

Of course, the present study does not afford any possibility of assessing the significance of the various immunizations to the hearing organ. It also gives no definite information as to what the function of hearing would have been, had the infants survived. A comparison with temporal bones from infants without erythroblastosis foetalis indicated that the haemorrhages in the peripheral hearing organ were of the same extent and spread in the two groups.

The most severe immunization and the most severe damage to the brain stem were found in Case 1. This patient was severely anaemic, but had no yellow pigmentation in the characteristic nuclear areas and a fairly low serum level of bilirubin. Comparison with Case 5 was interesting as this latter patient had a normal haemoglobin level, but a high serum bilirubin and no definite degenerations in the auditory nuclei.

Thus, in our opinion, the demonstrated brain damage is of anoxic genesis, and does not appear to have been caused directly by the increased serum bilirubin.

ZUSAMMENFASSUNG

Nach einer kurzen Übersicht klinischer und pathologisch-anatomischer Arbeiten über den Einfluss des Erythroblastosis foetalis auf das Gehörorgan werden Krankheitsgeschichten und pathologisch-anatomische Funde von vier neugeborenen Kindern mit verschiedener Bluttypimmunisierung und einem Patienten mit Hyperbilirubinämie infolge Leberschädigung mitgeteilt. Die Pathologie des Schläfenbeins unterschied sich nicht besonders von jenen, die bei den entsprechenden Patienten ohne Morbus Hämolyticus Neonatorum demonstriert wurden. In den

Horkernen wurden perivaskulare Blutungen und zerstreute Ganglienzellen Degenerationen gefunden, aber die Veranderungen traten mit ebenso grosser Haufigkeit in den basalen Gehirnabschnitten und Gehirnstamm vor Die kurze Lebenszeit der Kinder war eine wahrscheinliche Ursache dazu dass Gelbpigmentierung in dem Zentralnervensystem bei den vier immunisierten Patienten nicht nachgewiesen werden konnte Die pathologisch anatomischen Funde ermoglichten es nicht die Einflusse des Erythroblastosis und der Geburtsschaden auf das Gehororgan zu unterscheiden

Nach unserer Meinung ist die Wirkung des Erythroblastosis auf das Gehororgan eher der anamisch anoxische Insult als ein direkter toxischer Schaden durch Bilirubin

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TRANSLABYRINTHINE OPERATION ENFORCED BY EXTENSIVE EAR PROCESSES

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Tumors originating in the petrosal bone may extend into the cerebral cavity. In these cases, without knowing this beforehand, the ear surgeon will be obliged to tresspass the traditional borders of his speciality. In the last 5 years in 3 patients two neuroma and one cholesteatoma were successfully extirpated through the translabyrinthine approach.

Tumors, cholesteatomata and of course abscesses originating in the middle ear, mastoid and petrosa mostly develop inside the temporal bone but occasionally they may also break through the cortex and extend into the cerebral cavity. In such cases, during operation and without prescience, the ear surgeon will be compelled to follow the tumor past the traditional boundary of our speciality. The opening of a brain abscess by following the pathway of the infection out of the mastoid through the dura mater into the brain is a relatively simple example of this kind of surgery. It is more seldom that extensive tumors and cholesteatomata are operated with success.

A patient from whom we removed a neuroma from the mastoid died two years later because of an overlooked cerebral extension. This induced us to search in similar cases for such extensions. If such a condition is met with for the first time, an approach must be improvised, the technic of which will stabilize as the surgeon operates more of these cases. In my opinion, because they are relatively seldom, it is recommendable to report them, especially after the very important work on ponto-cerebellar tumors done by House. In the last 5 years we have seen three of them, at a time that we had not yet read his work.

CASES

Mrs. v. M. v. W., born in 1914, was committed to our clinic in March 1961 because of a paresis of the left facial nerve. This had started in June 1960 after she had had twitches in this half of her face. Since her 9th year the

Herrn Prof. Dr. F. Zöllner zu seinem [illegible] Geburtstag mit großer Bewunderung und mit vielem Dank gewidmet.

patient had had a dry cavity after radical operation The left ear was deaf and the labyrinth insensitive The patient had no pain Surprisingly enough the X ray photo showed an extensive destruction of the petrosal bone suggesting an unoperable malignant tumor Together with the neurologist the neurosurgeon and the radiotherapist palliative radiation was considered For this the type of tumor should be known As it was probable that the Eustachian tube was involved it was assumed that a biopsy could be obtained from this organ Consequently small forceps were introduced from the ear through the isthmus into the tube To everyone s pleasant surprise the tumor appeared to be a cholesteatoma probably a relapse of the same trouble she had had in her youth

On March 20th 1961, an exploration was decided upon in order to remove the process if possible along the same lines as it had originated—by clearing away the petrosal bone After removing the bony border and laying bare the labyrinth block the cholesteatoma bulged out into the operation area The facial nerve was found and with the help of the microscope it was taken out of the labyrinth block For the greater part this block and the part between the squama mastoidea and the jaw joint were removed Only a bony ridge around the bend of the facial nerve was left for support Thus a wide approach resulted through which the cholesteatoma situated between the dura and the hindmost and middle cranial groove could be removed Near to the point of the petrosal bone the cholesteatoma had grown through the arachnoidea After removal there remained a defect of 3 5 cm from where a clear liquid welled up The facial nerve was intact and could be followed up to the place where it left the brain stem The acoustic nerve appeared to have been destroyed completely Gelfoam was laid on the defect in the arachnoidea

In the following weeks the patient s temperature varied from very high to normal Coagulating staphylococcus aureus and B coli were cultivated from the operation wound After consulting our bacteriologist the patient was treated with rolitrecycline (Reverin) and methicilline (Celbenin) but her condition worsened steadily

On inspection of the wound small incidental cholesteatoma particles were seen For this reason it was decided after consulting all specialists involved to re operate concentrating now on the only part which could not be seen properly in the previous operation—namely the hindmost and underneath part of the processus mastoideus On June 13th a walnut sized offshoot of the original cholesteatoma was found in and underneath the mastoid of which the lower bony wall was missing The facial nerve was looked for near to the foramen stylomastoideum and again loosened from the cholesteatoma up to the bend of the Fallopian canal The tumor was then removed completely After this the temperature dropped and the patient recovered quickly In the course of the following year the function of the facial nerve recovered for the greater part and now she is in perfect health and has no trouble from the one missing labyrinth

After this successful case with the same technic we operated two other patients suffering from neurinoma originating from the temporal bone

Mrs J v d W J was born in 1934 After having had headaches for years she became more and more deaf in her right ear with tinnitus and spells of dizziness In February 1962 she developed a right sided peripheral facial nerve paralysis

There were also difficulties in swallowing. Her voice became hoarse and she could not call out any more. In December 1962 she was committed to the Department of Neurology, where a right-sided paresis including the VII to XII nerves was established. Based on this finding a process in the right ponto cerebellar angle, extending in the direction of the foramen magnum, was assumed On X-ray examination a destructive process was found in the base of the skull on the medial side of the foramen magnum, continuous of the medio distal part of the front half of the right pyramid Blood, urine and lumbar liquid were normal The rate of blood sediment was 19–47 mm, the electro encephalogram showed diffuse abnormalities

On otological examination, through the intact ear drum in the lower half of the middle ear cavity, abnormal tissue was discovered Consequently the middle ear cavity was explored by means of cutting around and flapping up the ear drum The result of a biopsy was "probable neurinoma". In consultation with the neurologist, the neurosurgeon and the rontgenologist it was decided that we should operate the patient by means of the trans-labyrinthine approach This in order to confirm the diagnosis and if possible to extirpate the tumor

On January 23rd, 1963, the mastoideum and the middle ear cavity were explored The tumor filled the middle ear cavity The bone of the squama above the tumor was still intact, towards the front and behind the tumor the bone had disappeared A probe could easily be inserted for about 6 cm, measured from the bend of the facial nerve The tumor had a compact wall which surrounded a cavity, which was filled with a yellowish slimy substance. This smeared out and gave a fatty impression The wall of the tumor consisted of neurinome tissue

A trans labyrinthal pathway through the promontorium was made, drilling away the semi-circular canals, carefully avoiding the facial nerve In this way we succeeded in exposing the tumor After dissection of the meninges it was possible to remove the tumor *in toto* The facial nerve could be observed up to the brain stem The acoustic nerve and the whole point of the petrosal bone were missing During the first fortnight some clear yellow liquid came out of the wound, then a quick recovery followed The patient was discharged on February 19th, 1963, in good condition In the course of the year the nerves recovered, the facial nerve functioning satisfactorily, the vocal chords moving symmetrically and the function of the palatum and swallowing becoming normal

Mrs M B N, born in 1906, was committed to the department of neurosurgery in October 1964 because of a slowly developing peripheral paralysis of the right facial nerve On neurological inspection only a positive Babinsky on the left side and a positive reflex of Mayer on the left side were found The total protein content of the spinal fluid was 33 mg/100 ml with 63 cells and normal gold and benzoesol curves The X ray examination of the cranium and petrosal bone did not show any abnormalities The consulting internist did not find anything ab normal, except a heightened blood sedimentation

On otological examination a conductive hearing loss of 20 dB was found The vestibular reactions were normal As in the previous patient here, too, by in spection of the right ear drum abnormal tissue was seen off the oval window. It was decided to explore the middle ear and for this the patient was moved to the department of otology

On October 30th the ear drum was endaurally flapped back. A yellowish smooth tumor was found in the atticus. The long bone of the incus had been destroyed. The atticus was enlarged by using a drill. The tumor, in so far as visible was removed. Against our expectations the bony facial nerve canal appeared to be intact up to the processus cochleariformis. Consequently the facial nerve paralysis was not explained. The conductive hearing loss was considered to be primarily due to the interrupted ossicular chain. However, in this condition a loss of 60 dB should be found. As the conductive loss was only 20 dB it was assumed that the tumor, connecting the oval window to the tympanic membrane provided sound transmission. At this stage it was decided to wait for a possible improvement before exploring the central part of the facial nerve along the retro auricular and trans labyrinthal approach and thus sacrificing hearing. The tumor appeared to be a neurilemmoom assumedly of the facial nerve.

As there was no improvement in November 1964 a retroauricular mastoid operation was performed during which the tumor became visible in the atticus. Then the bone above the labyrinth block was drilled away until the ganglion geniculi was exposed. The central part of the facial nerve had been completely taken up in the tumor. After the horizontal and upper canals were removed it was easy to remove the marble sized tumor in small parts using a loop wire and a spoon. The growth appeared to lie on the point of the petrosal bone and bulged out into the middle cranial groove. Careful revision did not give any more tumor tissue. The arachnoidea which was still completely intact filled the cavity. The patient was discharged on December 5th 1964 and is still in perfect health. In the spring of 1965 a facial hypoglossus nerve anastomosis was done (Dr Luyendijk) and at the end of the year function was restored.

DISCUSSION

In these three cases we were compelled to follow the translabyrinthal lines in order to reach the endocranial part of the tumor. W. F. House (1964) recommended the same approach for tumors of the acoustic nerve and of the ponto cerebellar angle tumors which do not primarily start out from the petrosal bone.

In his large material complications and deaths occurred relatively seldom. The post operative condition of his patients seems to be good which cannot always be said for patients operated by the classical sub occipital approach. The sizes of the tumors found by House varied from 1-4 cm. The large tumors often had to be reduced by removing pieces intercapsularly as we did in our second case. If some tumor remains this is not lethal because they grow slowly and are benign.

Now that otological and rontgenological diagnostics are becoming better and better we will be able to diagnose these tumors when they are still small. House's results are so encouraging that this technique will probably be followed up elsewhere.

With these difficult micro surgical operations in a marginal area, close co operation of otologist neurologist rontgenologist audiologist and neuro-

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EXPERIMENTAL STUDIES ON SOUND TRANSMISSION IN THE HUMAN EAR

VII The influence of Age and Post Mortem Factors

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Age and certain post mortem factors have been investigated and found to have apparently no systematic effect upon measurements of sound transmission in human temporal bone preparations

INTRODUCTION

In our series of studies on sound transmission in the human ear (Andersen *et al* 1962 1963) the utility of temporal bone preparations in the investigation of normal and pathological middle ear function has been demonstrated The present work considers certain factors which could conceivably influence the reliability and validity of results obtained in these and similar investigations

1 Age of the patient at the time of death There is cyclical reference to the notion that the functional health of the middle ear mechanism changes with progressing age In order to affect the transmission of sound through the middle ear such change would have to be structural in nature and would presumably remain after death The presence of these structural differences would tend to bias measurements obtained on a sample of specimens from patients differing greatly in age at the time of death

2 Time interval between death and the first measurement of transmission For several reasons it is not possible to obtain prepare and measure sound transmission in specimens on any regular time schedule As this interval between death and measurement is subject to wide variation differences in the progress of post mortem changes during this period provide another potential source of bias

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surgeon is necessary for the benefit of the patient in order to determine what has to be done and by whom. The dynamic development of our profession brings with it that each time there has to be a re-orientation of old view points.

It is worth mentioning that already in 1911 the Dutchman Quix, following the otologist Panse, had made a similar attempt and had removed a pea-sized tumor. The patient died, however, some months later because the removed growth appeared to be a small part of a much larger tumor.

The fact that bounds are overstepped or rather that they are being shifted is not only found in the ear. The trans-ethmoidal hypophysis operation, which, it is true, is an older intervention, is being used with success by various rhinologists and neurosurgeons. Here too it is logical that the entrance through the ethmoid and the sinus sphenoidales offers many advantages. Similarly carcinoma of the nose and its cavities sometimes forces us to operate on the cranial base and to resect the upper jaw and sphenoid.

Not so long ago such approaches were thought to be inadvisable. Now, thanks to the ear microscope, the perfect lightning and suitable instruments, the skilled surgeon, who possesses a thorough knowledge of anatomy, may surpass the traditional borders of his speciality successfully.

RÉSUMÉ

Des tumeurs et cholestéatomes qui naissent dans l'os pétreux peuvent s'étendre dans la cavité crânienne. Sans qu'il le sache d'avance le chirurgien de l'oreille sera parfois obligé de passer les limites usuelles de son domaine. Pendant les cinq dernières années trois malades, deux souffrant de neurinomes et un de cholestéatome, chez qui pour cette raison la route translabyrinthaire devrait être suivie, étaient opérés avec succès.

ZUSAMMENFASSUNG

Geschwulste und Cholesteatomen, die im Felsenbein anfangen, konnen bis in die Schädelgruben auswachsen. Ohne dies im voraus zu wissen, kann der Ohrenchirurg gezwungen werden die ublichen Grenzen seiner Spezialität zu überschreiten. Während der letzten funf Jahre haben wir zwei Neurinomen und ein Cholesteatom erfolgreich translabyrinthär exstirpiert.

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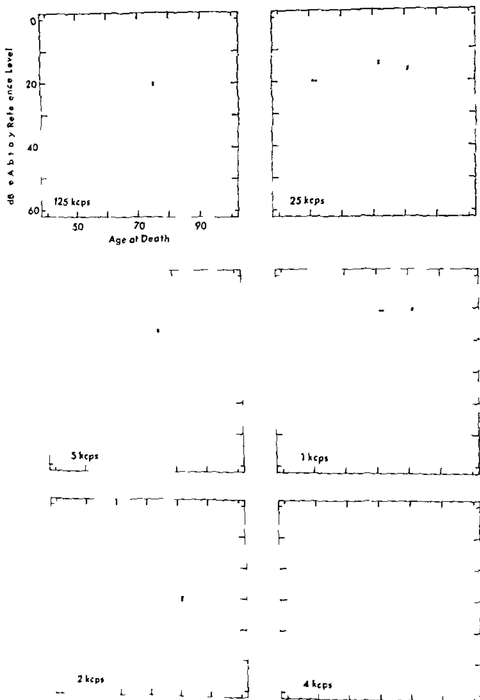


Fig 1 Relationship between sound transmission measurements in temporal bones and age of the patient at the time of death (Each point represents the level of sound transmission measured in one preparation at the frequency indicated)

3. Desiccation during the experiment. An experiment begins with the measurement of sound transmission in a specimen which has been prepared in a standardized manner. In the segment of time between this moment and the final measurements, post-mortem changes undoubtedly continue. Perhaps the most obvious of these are associated with desiccation, the "drying out" so often invoked in criticism of temporal bone experiments. Our series of sound transmission studies has been conducted on the premise that drying and other changes occurring during the period of experimentation have little or no influence on our measurements. Evidence to the contrary would severely limit the clinical applicability and value of information gained in these studies.

Although literally hundreds of specimens have now been used without any observable indication that the above factors are of consequence, the questions nonetheless appear to require a specific reply. This is the purpose of the present work.

PROCEDURE

With reference to the first two factors, a series of 28 human temporal bones were prepared and their transmission characteristics measured using methods described most recently by Elpern, Greisen & Andersen (1965). The age of each patient and the interval between death and the first measurement of sound transmission were noted. The time lapse between the actual removal of the temporal bone and the first measurement remained fairly constant at 2–3 hours. The third factor was approached by preparing the specimen in the usual way and exposing it to the usual test environment (25 degrees Celsius) for a period of three hours, during which sound transmission was measured at 20 minute intervals. Pathological ears were excluded from the material.

RESULTS AND DISCUSSION

Measurements pertinent to the first two factors are shown in Figs. 1 and 2. Each point plotted on these graphs denotes the level of sound transmission, scaled in dB relative to an arbitrary reference, measured on one preparation at the frequency indicated. The absence of any clearly distinguishable slope in the patterns of measurements suggests either that these factors have no influence on sound transmission or that their influence is obscured by other factors, such as inherent anatomical differences or subtle, largely uncontrollable differences in the preparation procedure. It is sufficient for present purposes to note that neither age nor the time interval between death and measurement in themselves appear to exert any significant effect. The insignificance of the third factor is evident in the finding that measured changes in transmission during the three hour experimental period attained a *maximum* of only 2 dB at any frequency.

ZUSAMMENFASSUNG

Messungen des Schalleitungsvermögens des postmortal entfernten menschlichen Schläfenbeines zeigten dass solche Faktoren wie a) Alter des Patienten b) Zeitdauer zwischen Tod und Experiment und c) Eintrocknung während des Versuches kaum einen Einfluss auf die Schalleitung hatten

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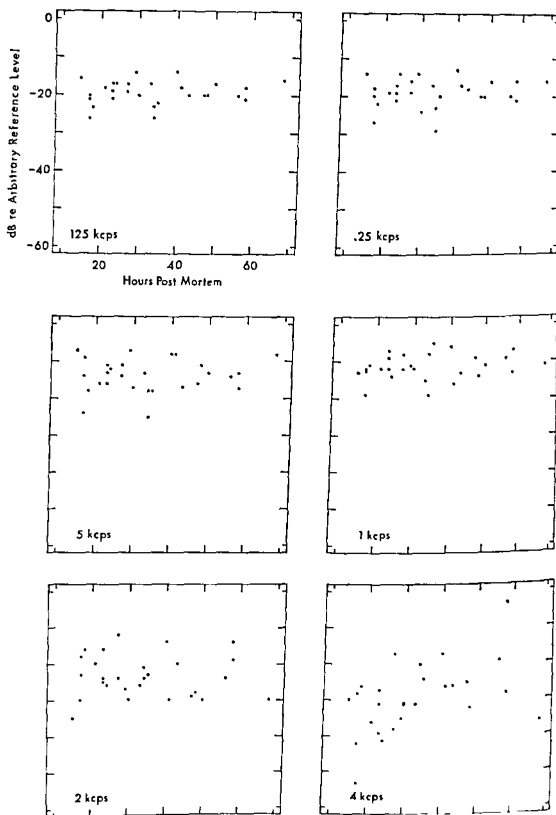


Fig. 2. Relationship between sound transmission measurements in temporal bones and the number of hours elapsed between death and measurement. (Each point represents the level of sound transmission measured on one preparation at the frequency indicated.)

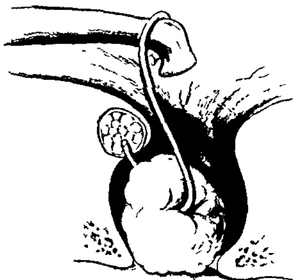


Abb 1 Schuknecht-Drahtprothese aufgeworfen und in den Facialisstamm eingespiesst

gang zur Fussplatte stark einengen kann Wir wissen auch, dass gerade in diesem Verlaufsabschnitt ausgedehnte Dehiszenzen des Falloppischen Kanals bestehen können Dietzel hat jungst hierüber erneut eingehend berichtet So sind Läsionen des Nerven bei der Entfernung der Stapesfussplatte Ereignisse, die im Bereiche des Operationsrisikos liegen können, sie sind nicht einmal ungewöhnlich

Nachfolgend soll jedoch von einer höchst merkwürdigen Art der Verletzung des Gesichtsnerven gesprochen werden Einer Läsion mit Lähmungsfolge durch Einspiessung des aufgeworfenen Drahtendes einer Schuknechtprothese in den Nervenverlauf

E. Erna Krs Bl Nr 133/1964, Univ HNO-Klinik, Göttingen Wegen Paukensklerose wurde auswarts zweizeitig operiert Im ersten Eingriff wurden nach Angaben des einweisenden Otologen sklerotische Massen im Bereiche zwischen Facialis-Hammer-Amboss und ovalem Fenster entfernt, die Crurotomie vorgenommen, die Superstruktur des Steigbugels an der Stapediussehne vorubergehend in das Hypotympanon verlagert und die Pauke mit einem Fascientransplantat geschlossen Im zweiten Eingriff wurde die Fussplattenresektion durchgefuhrt und — nachdem die zuvor geplante Wiederverwendung der Stapes-Superstruktur nicht ratsam erschien — eine Schuknecht-Drathprothese aus V 2-A-Stahl mit Bindegewebs-Pflock als Stapesersatz verwendet Die bis zu diesem Zeitpunkt völlig intakte Facialis-Funktion war unmittelbar nach der Operation verloren Es bestand eine

ZUR VERWENDUNG VON STAHLDRAHTPROTHESEN ALS STEIGBÜGELERSATZ

Beachtenswertes zur Vermeidung unerwünschter Folgezustände

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Bericht über eine Facialisläsion, entstanden durch fehlerhaftes Einbringen einer Schuknecht-Prothese. Der zu lang abgeschnittene Stahldraht hatte sich aufgeworfen; sein Ende gelangte durch eine Dehiszenz des überhangenden Falloppischen Kanals in den Facialisstamm. Die Eigenart der Verletzung lässt auf direktem Wege eine Bestätigung früherer Untersuchungen über die Topographie des Faserverlaufes im Facialisstamm zu.

Verletzungen des Gesichtsnerven im Verlaufe otochirurgischer Eingriffe sind bekannt. Im Schrifttum differieren die Angaben hierüber zwischen 1,6 (Pöllmann, 1937) bis 3,7% (Körner, 1892) aller Operationen. Bei Nachoperationen ist die Gefahr einer Läsion stets etwas höher einzuschätzen, nach Zühlke (1956), bis zu 11%. Die grundsätzliche Verwendung der Lupenbrille und des Operations-Mikroskopes bei der Durchführung von Operationen am Ohr lässt erwarten, dass die Anzahl intraoperativer Verletzungen des Gesichtsnerven abnimmt.

Es sind typische Stellen, an denen solche Verletzungen entstehen. Die Lokalisation ist im allgemeinen abhängig von der Art des ausgeführten Eingriffes. Im Falle der Mastoidektomie wird der Nerv besonders in seinem vertikalen Verlaufsabschnitt zwischen Proc. pyramidalis und Foramen Stylomastoideum betroffen. Bei Radikaloperationen ist das zweite Facialisknie bei der Glättung des Spornes besonders gefährdet. Auch operationstechnische Schwierigkeiten im Verlaufe von tympanoplastischen Eingriffen können Anlass zu Verletzungen des Gesichtsnerven sein (Jongkees 1956, 1958, Kettel, 1959, Miehlke, 1960) und nicht ausgeschlossen hiervon bleibt die Stapesplastik, obgleich der Operateur den Facialisverlauf hierbei stets im Blickfeld hat. Wir wissen, dass sich der Gesichtsnerv in seinem tympanalen (horizontalen) Verlaufsabschnitt nicht selten mehr oder weniger stark über das ovale Fenster vorbuckelt und den Zu-

Herrn Professor Dr. P. Falk zum 60. Geburtstag in Dankbarkeit gewidmet

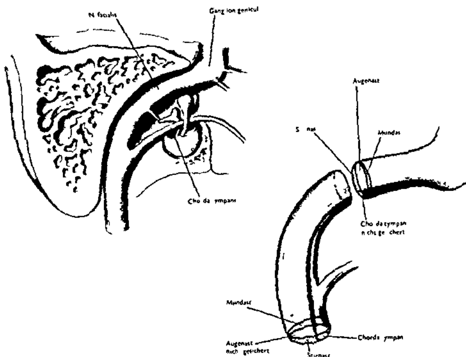


Abb 4 Topographie des Faserverlaufes im Facialisstamm (aus Miehlke, A, „Die Chirurgie des Nervus Facialis" Urban & Schwarzenberg München-Berlin 1960)

eingespiesstes Drahtende aus dem Gesichtsnerven entfernt Das ovale Fenster wird anschliessend mit einem Stückchen Bindegewebe nach Zangemeister-Heermann verschlossen Das vom Voroperateur im 1 Eingriff eingeheilte Ersatztrommelfell muss geopfert werden Ein neues Fascientransplantat wird gewonnen, der Amboss um seine Langsachse rotiert und als Columella zwischen Bindegewebspfropf und neuem Fascien-Trommelfell eingeschaltet (modifizierte Plastik Typ III nach Wullstein, 1957) Zur oberen Stutze der Columella wird der überhängende elastische Facialisnerv benutzt (Heermann, 1964) Nach Abschluss der Operation Umgangssprache 3 m Nach 24 Stunden kann die Patientin die Augenlider aktiv schliessen, eine leichte Nasolabialfalte deutet sich an Im Verlaufe mehrerer Monate kommt es zu einer weitgehenden, wenn auch nicht ganz vollständigen Funktionswiederkehr, allerdings mit Massenbewegung (Abb 2 und 3)

Diese Verletzung ist in zweierlei Hinsicht lehrreich

1 Es ergibt sich eine Bestätigung der von Neumann (1906), Pöllmann (1937) Hofmann (1924), Miehlke (1960) auf verschiedenen Wegen ermittelten Topographie des Faserverlaufes im Facialisstamm insoweit dies den Stirnast betrifft Dieser liegt nach unseren Untersuchungen im tympanalen Verlaufsabschnitt der Hinterwand des Facialiskanales an (s



Abb. 2. Traumatische Facialislähmung (Drahteinspiessung) 5 Wochen lang bestehend. Abb. 3. 6 Monate nach Revision und Drahtentfernung.

vollständige Lähmung vom peripheren Typ. Diese hatte sich nach 5½ Wochen nicht zurückgebildet. Die elektrischen Prüfungen liessen auf eine schwere Verletzung schliessen, es erfolgte die Klinikseinweisung nach hier zur Revision.

Klinisch: Komplette Facialislähmung links. Kein Spontan- und Provokationsnystagmus. Umgangssprache 2 m. Die elektrische Untersuchung des N. VII (Chronaximetrie, Akkomodabilitätsbestimmung und Elektromyographie) ergaben insgesamt gesehen eine schwere Schädigung, doch ist anzunehmen, dass keine vollständige Durchtrennung (Neurotmesis) des Gesichtsnerven vorhanden ist. Dabei scheint der Stirnast von der Läsion am schwersten betroffen.

Revision (25.3.64, Miehlke): Es ergibt sich, dass die Wand des Fallopischen Kanals über dem ovalen Fenster unversehrt ist, es bestehen einige kleinere Dehiszenzen. *Durch eine solche kleine Lücke an der dem ovalen Fenster zugekehrten Seite des Fallopischen Kanals hat sich das aufgeworfene etwas zu lang abgeschnittene distale Ende der Schuknecht-Drahtprothese in den N. VII eingespiesst.* Die Einspiessung erfolgte in jenem Teil der Nervencircumferenz, welcher der Unterwand des Facialiskanals anliegt (Abb. 1). Diese Lokalisation entspricht der Verlaufsregion des Stirnastes. Die knöcherne Hülle des Fallopischen Kanals wird bis zum Ganglion geniculi abgesprengt, der Nerv quillt daraufhin dem Operateur entgegen. Die Schuknecht-Prothese wird aus dem ovalen Fenster und ihr

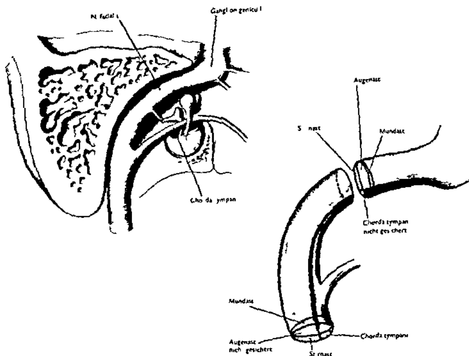


Abb 4 Topographie des Faserverlaufes im Facialisstamm (aus Miehlke, A., „Die Chirurgie des Nervus Facialis" Urban & Schwarzenberg München-Berlin, 1960)

eingespiesstes Drahtende aus dem Gesichtsnerven entfernt Das ovale Fenster wird anschliessend mit einem Stückchen Bindegewebe nach Zangemeister-Heermann verschlossen Das vom Voroperateur im 1 Eingriff eingeheilte Ersatztrommelfell muss geopfert werden Ein neues Fascientransplantat wird gewonnen, der Amboss um seine Längsachse rotiert und als Columella zwischen Bindegewebspfropf und neuem Fascien-Trommelfell eingeschaltet (modifizierte Plastik Typ III nach Wullstein, 1957) Zur oberen Stütze der Columella wird der überhängende elastische Facialisnerv benutzt (Heermann, 1964) Nach Abschluss der Operation Umgangssprache 3 m Nach 24 Stunden kann die Patientin die Augenlider aktiv schliessen eine leichte Nasolabialfalte deutet sich an Im Verlaufe mehrerer Monate kommt es zu einer weitgehenden, wenn auch nicht ganz vollständigen Funktionswiederkehr, allerdings mit Massenbewegung (Abb 2 und 3)

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Abb 4) Die Einspiessung der Drahtprothese erfolgte in diesem Teil der Nervencircumferenz (Stirnast) Der klinisch sowie elektromyographisch vor der Revisionsoperation ermittelte schwerste Grad der Schädigung unter den 3 Hauptästen des Gesichtsnerven betraf den Stirnast Dies ermöglicht somit eine direkte Bestätigung der früher erhobenen topographischen Zuordnung der Faserverläufe

2 Für die Praxis der Stapesersatzplastik mit der Schuknecht-Drahtprothese ergibt sich der Hinweis, dass beim Abschneiden des über dem Bindegewebspflock geknüpften distalen Drahtendes grösste Sorgfalt walten sollte Insbesondere darf das Drahtende nicht im geringsten aus dem Bindegewebspflock herausragen, es sollte ganz knapp am Knoten innerhalb des Bindegewebes abgeschnitten werden, so dass ein Aufwerfen und Einspiessen des Drahtes mit seinen für den Gesichtsnerven verhängnisvollen Folgen beim Einpflanzen in das ovale Fenster nicht entstehen kann

SUMMARY

A facial lesion due to a badly fitted Schuknecht prosthesis is described The end of the steel wire, which had not been sufficiently shortened and had sprung upwards, entered the facial region through an opening in the overhanging fallopian canal The peculiarity of the injury confirms earlier investigations into the topography of the fibrous distribution in the facial area

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Eingegangen am 31 August 1965

PERIODICITY ANALYSIS IN THE GUINEA PIG COCHLEA

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In guinea pigs cochlear microphonic responses were studied during stimulation with harmonic high tone complexes In the apical portion of the cochlea a sine wave with the frequency of the missing fundamental could be recorded The amplitude of this low frequency microphonic potential (CM) in the third turn of the cochlea appears to be about equal to the amplitude of the strongest component of the high tone complex recorded in the basal turn The missing fundamental appears to stimulate the apical portion of the cochlea which indicates cochlear analysis according to a certain place principle although apparently not the Fourier principle

INTRODUCTION

A harmonic complex consisting of high tones with a constant frequency difference from which complex the eventual low components have been removed by careful filtering still produces a dual tonal impression in which the high frequency complex is perceived with a corresponding high pitch but apart from that a low pitch can be heard even at sound levels far below distortion threshold The periodicity of such an acoustic signal is likely to be responsible for the perception of this low pitch This was described by Schouten as the Residue phenomenon in 1940 elaborated by de Boer (1956) and recently summarized by Schouten Ritsma & Lopes Cardozo (1962)

Thus Schouten s residue became the principal argument in the discussion between supporters of place and volley theory A detailed review of the evidence available about this problem is given by Licklider (1962) When surveying these data most experimental work about this subject appears to be done by correlating the relation between acoustic input and sensation (Thurlow & Small 1955 Licklider 1956 Kylstra 1964 Schouten 1940 The function of the individual parts of the auditory system during this kind of stimulation however has been studied only in a few instances (von Bekesy 1961 Deatherage Davis & Eldredge 1957) Thus the locus of origin of this periodicity pitch discrimination has not been established clearly although a neural pitch extractor is mentioned generally (Schouten 1962 Licklider 1962)

PROCEDURE

In the experiments to be described in this paper investigations have been performed into the electrical cochlear responses during stimulation with high tone complexes. In this way it is possible to gain an insight into the cochlear stimulation pattern, the cochlear microphonic potential giving a picture of the movements of the basilar membrane. By recording the CM in different parts of the cochlea, a rough determination of the place of origin of the ensuing microphonic effects can be made.

Anesthesia and Operation

Adult guinea pigs are anesthetized by intraperitoneal injection of 100 mg/kg eunarcon and 0.02 mg/kg scopolamine. During the initial period artificial respiration is usually necessary, but recordings are made under light anesthesia and spontaneous respiration. The cochlea is approached through the bulla tympanica as described earlier (Leibbrandt, 1965). Electrodes are introduced into the scala tympani of the basal and third turn of the cochlea through drilled holes as described by Davis *et al.* (1949). The cochlear potentials are measured against an indifferent electrode implanted under the skin of the neck.

Recording

Tektronix preamplifiers type 122 are used in the two separate channels. The output of the basal and third turn is displayed on an oscillograph, while analyzation is performed at the same time with a frequency analyzer (Bruel & Kjaer type 2105). The same frequency analyzer with an artificial ear (condenser microphone) is used to record the sound level during these experiments.

Stimulation

The output of a pulse generator (250 cps) is led through a band-pass filter adjusted at 4000 cps, an audio-amplifier, and a second adjustable filter (Allison type 2-B) with high and low cutoff at 4000 cps. This frequency band is well suited to the insert telephone receiver (Philips PH 7) and gives a strong sensation in the frequency of the missing fundamental.

All measurements to be reported in this paper were performed with the aforementioned stimulation pattern (Figs. 1 and 2). In later experiments with a small insert condenser telephone receiver, which is available nowadays, is was possible to produce harmonic high tone complexes in higher frequency regions. The results in these experiments appear to be in accordance with the measurements with the 4000 cps frequency band. In Figs. 3 and 4 some recordings of these experiments are shown. Note the similarity of the electrical signal and the acoustical signal as recorded with the artificial ear. With the condenser telephone receiver this resem-

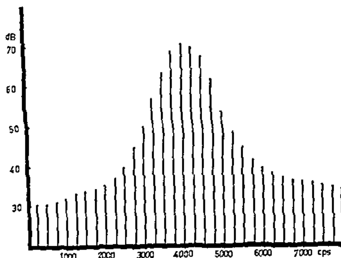


Fig. 1. Frequency spectrum of the stimulating sound used in these experiments at 0 dB re 10^{-16} watt/cm² of the strongest component as recorded with condenser microphone and frequency analyzer.

blance is rather good generally but the hearing aid telephone can distort the pattern considerably, therefore frequencies must be selected with care.

In all experiments the sound level (in dB re 10^{-16} watt/cm²) of the 4000 cps component of the high tone complex is used as reference, as recorded with the frequency analyzer. This is an inaccurate measurement however different sound level recorders giving different results with pulsed tones (Niese 1961). In our case the sound level indicated by the frequency analyzer was nearly identical with the (human) sensation level. Analy-

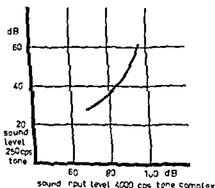


Fig. 2. The relation between the sound level of the strongest component of the high tone complex (4000 cps) and the presence of the fundamental (250 cps) in the stimulating s und. At the level of about 80 dB of the 4000 cps component the fundamental appears in the analysis due to distortion in the telephone receiver (Philips PH 7), but the level of the 250 cps component is 40 dB lower.

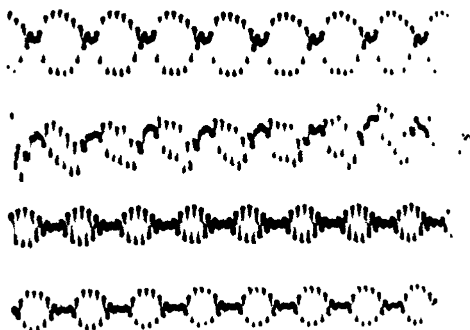


Fig. 3. Cochlear potentials due to stimulation with a high tone complex (7000 cps band). Upper trace: CM recorded from the basal turn. Second trace: CM recorded from the third turn of the cochlea. Third trace: Electrical signal. Bottom trace: Acoustical signal of the condenser telephone receiver recorded with the artificial ear. The repetition frequency of the tone burst in this recording is 875 cps.

zation of the stimulating sound reveals the picture of a high tone complex (Fig. 1), but at 80 dB re 10^{-16} watt/cm^2 the fundamental appears in the acoustic pattern due to distortion in the earphone, below 80 dB, however, no low frequency components are present in the stimulus (Fig. 2).

Experiments

20 guinea pigs with electrodes properly fitted in basal and third turn without further noticeable structural damage to the cochlea were stimulated with high tone complexes. In all experiments a distinct microphonic effect in the frequency of the missing fundamental has been recorded just as in earlier experiments by Deatherage, Davis & Eldredge (1957), although their threshold values were much different. The low frequency sine wave is present not only in the basal turn, which is more sensitive for high frequencies, but even better in the third turn, which is more sensitive for low frequencies (Figs. 3 and 4). In this very place of the cochlea the intensity of this low frequency is 10–15 dB higher than in the basal turn. It can be recorded even 30 dB below distortion level (80 dB) of the sound producing apparatus (Fig. 2), at which level no energy in the frequency of the fundamental can be detected in the stimulus.

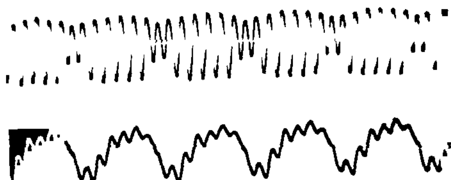


Fig. 4. As Fig. 3 with 4000 cps band, repetition frequency 570 cps. Upper trace: CM recorded from the basal turn. Lower trace: CM recorded from the third turn of the cochlea.

The different intensities of this low frequency signal in basal and third turn of the cochlea demonstrate that this effect must be generated in the apical portion of the cochlea, which excludes similar effects caused by summating potential (SP) on the place of the basilar membrane where the high tone complex is projected. The whole nerve action potential (AP) due to tone bursts is known to be generated mainly in the basal turn (Deatherage, Eldredge & Davis 1959) and is not recorded with large amplitudes in the third turn generally. In some of our experiments KCl was injected into the basal turn, which did not affect this low frequency response in the third turn until after some time all responses disappeared. The amplitude of this low frequency *sine wave is too large to ascribe it to* the SP; moreover, it rises together with the intensity of the stimulus to a maximum and decreases at still higher sound levels, which is characteristic for the CM. It was not possible to suppress this low component by masking, like the AP.

These observations demonstrate the existence of a cochlear microphonic effect in the frequency of the "missing fundamental", which is located in the apical portion of the cochlea.

In this way activity of the low frequency parts of the cochlea due to high tone complexes having been demonstrated, the relation between sound pressure level and intensity (in dB) of the CM of the fundamental (250 cps) and the strongest component (4000 cps) *of the high tone complex*

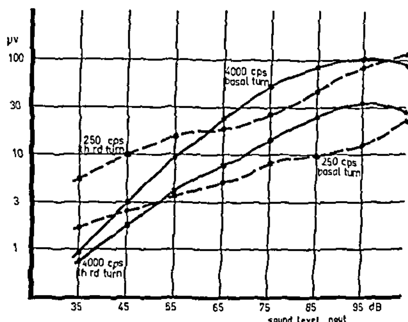


Fig. 5. The relation between the amplitude of the cochlear microphonic potential as measured with the frequency analyzer and the sound level of the 4000 cps component in dB re 10^{-16} watt/cm². Different electrode position and measured components of the cochlear responses are indicated. The fundamental is most marked in the third turn whereas the 4000 cps component dominates in the basal turn. Note the different slopes of the 4000 cps and 250 cps component.

has been studied, both in basal and third turn. In several experiments other combinations of stimuli were used producing the same results as before. Generally it is possible to record the CM between 40 and 100 dB (sound level of strongest component of the high tone complex).

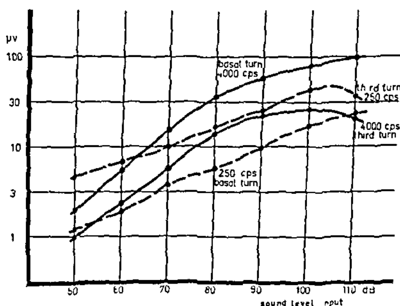


Fig. 6. Same as Fig. 5 in another experiment.

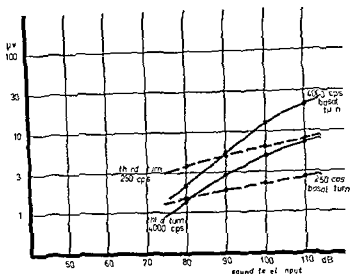


Fig. The same experiment as Fig. 6 after interruption of the ossicular chain. The telephone has been directed to the round window. The responses show the same pattern as Fig. 6 but at a lower sound level (30 dB difference)

Examples of measurements are given in Figs. 5–7. In all other experiments similar relations have been found. The relation between CM due to strongest component and sound pressure appears to be linear in all experiments just as the CM due to pure tones. The relation between the CM (apparently caused by the fundamental) and sound pressure is linear in some experiments. In others (about half of them) it was found that the amplitude of the CM increased proportionally to the square root of the sound pressure. It has not been possible to explain this variation in relationship between the experiments. Perhaps it is caused by differences of the fine structure of the acoustic stimulus.

Frequently the existence of the fundamental has been attributed to nonlinear distortion. In that case a quadratic relation between CM and sound pressure should be expected instead of a square root.

To eliminate distortion by the middle ear the stapes was detached from the incus in some experiments. The same relations were found (compare Figs. 6 and 7) but 30 dB weaker.

In fact the observations described in this paper exclude nonlinear distortion as the cause of the existence of the missing fundamental. Nonlinear distortion appears at sound levels of 70–80 dB at which levels the CM nearly reaches its maximum in these experiments. This means that even distortion of the sound producing apparatus is of minor importance for the perception of the fundamental of high tone complexes at high sound levels. Fig. 8 shows the relation with sound intensity of the CM due to the fundamental of a high tone complex and a pure tone both of a frequency of 250 cps recorded from the third turn of the cochlea. The pure tone appears

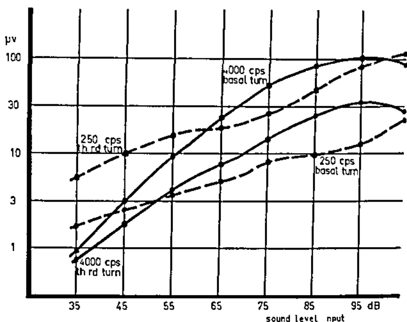


FIG 5 The relation between the amplitude of the cochlear microphonic potential as measured with the frequency analyzer and the sound level of the 4000 cps component in dB re 10^{-16} watt/cm² Different electrode position and measured components of the cochlear responses are indicated The fundamental is most marked in the third turn whereas the 4000 cps component dominates in the basal turn Note the different slopes of the 4000 cps and 250 cps component

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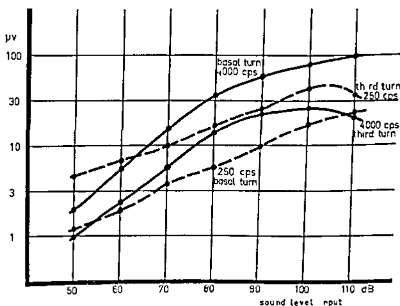


FIG 6 Same as Fig 5 in another experiment

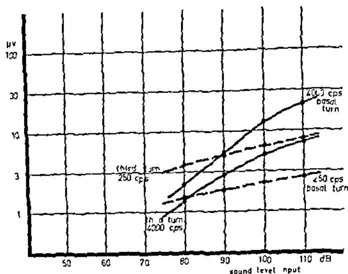


Fig 7 The same experiment as Fig 6 after interruption of the ossicular chain The telephone has been directed to the round window The responses show the same pattern as Fig 6 but at a lower sound level (30 dB difference)

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In fact, the observations described in this paper exclude nonlinear distortion as the cause of the existence of the missing fundamental Nonlinear distortion appears at sound levels of 70 80 dB at which levels the CM nearly reaches its maximum in these experiments This means that even distortion of the sound producing apparatus is of minor importance for the perception of the fundamental of high tone complexes at high sound levels Fig 8 shows the relation with sound intensity of the CM due to the fundamental of a high tone complex and a pure tone both of a frequency of 250 cps, recorded from the third turn of the cochlea The pure tone appears

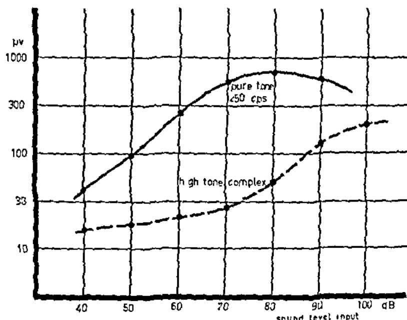


Fig. 8. The relation between amplitude of the cochlear responses and sound level of a 250 cps pure tone and the 250 cps responses due to a high tone complex as used in these experiments, both recorded from the third turn of the cochlea. The difference in amplitude amounts to 20 dB.

to have its maximum 15 dB higher than the fundamental of the high tone complex. This peculiar discrepancy is found in all experiments, but an explanation has not been found. Perhaps a slightly different vibration pattern of the basilar membrane causes this phenomenon. This speculation could play a part in the explanation of the absence of beats and masking of the residue.

Fig. 8 also shows the effect of distortion of the earphone at 70–80 dB. Only a rise of about 15 dB is seen in the graphic representation of the CM due to the fundamental.

In most experiments the output of the third turn of the cochlea during stimulation with high tone complexes has been studied after passing them through a low-pass filter. The low frequency CM appears to be inconstant, both in amplitude and in phase (Fig. 9). The significance of these variations has to be studied in future experiments.

DISCUSSION AND CONCLUSIONS

High tone complexes appear to drive the apical parts of the cochlea with a sinusoidal movement in the frequency of the fundamental, although no low frequency components are present in the Fourier spectrum of the stimulus. Apparently no Fourier analysis is performed by the cochlea, distortion being excluded in these experiments as possible cause of this phenomenon. Frequency analysis by localization along the basilar membrane has been demonstrated clearly, however. These observations on the cochlear microphonic potential are restricted to the movements of the

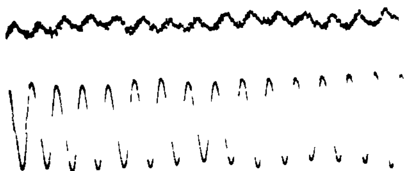


Fig 9 Output of the third turn of the cochlea when stimulating with a 4000 cps band (repetition frequency 250 cps) Upper trace unfiltered Lower trace the same signal after passing a low pass filter Note the irregularity of the sine wave

basilar membrane which demonstrates only one aspect of the whole chain of auditory perception In this respect our investigations are more limited than the experiments on a cochlear model with nerve supply (skin analogon) by von Bekesy (1961) The resemblance between these observations and the results of our experiments is, however striking

It must be stated that cochlear analysis according to a place principle does not exclude time measuring processes in the course of the transport of neural activity in the brain stem In fact many observations on binaural hearing, for example are pointing in that direction However impulses from different parts of the cochlea are involved when a high tone complex causes a dual pitch perception, the one high and the other low

ZUSAMMENFASSUNG

Die Reizfolgeströme der Schnecke wurden bei Meerschweinchen während Stimulierung mit durch Niederfrequenz modulierten hohen Tonkomplexen registriert In dem apikalen Teil der Schnecke wurde eine Sinuskurve mit der Periode dieser Niederfrequenz gefunden Die Amplitude dieses Reizfolgestromes mit niedriger Frequenz ist der Amplitude der stärksten Komponente des Hochtonkomplexes in dem basalen Teil der Schnecke ähnlich Der fehlende Grundton stimuliert also den apikalen Teil der Schnecke was der Analyse zufolge ein gewisses Ortsprinzip nachweist wenn auch nicht das Fourier Prinzip

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THE ADRENERGIC INNERVATION OF THE LABYRINTH

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Using the method of Falck and Hillarp for the histochemical demonstration of catecholamines, an adrenergic innervation is selectively shown in fresh tissue preparations of various parts of the labyrinth. Two different groups of adrenergic fibres are found: (1) A rich perivascular plexus continuous with the plexus of the basilar artery. It is only found around the labyrinthine artery and its greater branches. (2) An extensive adrenergic network in the lamina spiralis ossea and underneath the vestibular sensory epithelia independent of blood vessels. It forms a dense terminal plexus in the area of the habenula perforata. With selective transection of the vestibular, cochlear or entire VIII nerve it could be demonstrated that these adrenergic fibres originate in the central nervous system and reach the periphery with the cochlear nerve. A possible interpretation of their functional significance is presented.

An autonomic innervation of the labyrinth has been assumed for many years on the basis of clinical observations and anatomical studies. Monlandon (191[illegible]) emphasized a functional correlation between autonomic nervous system and inner ear. A direct effect of a lesion or experimental excitation of the stellate ganglion on the cochlear microphonics was demonstrated by Beickert, Gisselsson & Löfström (19[illegible]6). Racine (1942), Agazzi (19[illegible]) and Andrejzewski (19[illegible]) described autonomic nerve plexus (terminal plexus) in the membranous labyrinth using histological techniques of Stöhr, Boeke and Landau. Racine and Agazzi considered the fibres which are not associated with blood vessels as parasympathetic.

However, a final clarification of the question of the autonomic innervation of the labyrinth was hitherto not possible because the available histological techniques with silver impregnations proved to be unreliable (Hillarp 1946) and it was impossible to distinguish between adrenergic and cholinergic fibres. The results therefore were contradictory and offered no conclusive answers.

Recently Falck *et al.* (1962) developed a method for the direct histochemical demonstration of noradrenaline in fresh dried tissue or after

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freeze-drying Noradrenaline is a characteristic transmitter substance of the adrenergic nerve fibres The histochemical visualization of noradrenaline therefore allows a very selective demonstration of adrenergic nerve fibres

MATERIAL AND METHODS

The histochemical reaction is based upon the peculiarity of the catechol amines (adrenaline, noradrenaline and dopamine) and certain tryptamines, such as serotonin, to form a fluorescent compound if treated with formaldehyde The maximal fluorescence is observed in the blue light of about 405 mμ When using a barrier filter up to 500 mμ the fluorescence of the catecholamines is green to yellow-green and the one of serotonin is yellow. With a different filter combination an even better differentiation of catecholamines and serotonin is possible (Angelakos, 1964) *Noradrenaline* and dopamine on the one hand and adrenaline on the other can be distinguished by the reaction time We exposed the tissues during one hour to formaldehyde vapor, in which time only noradrenaline and dopamine react

Freeze-drying does not apply very easily to the histological preparation of the labyrinth, mainly because of the difficulty in decalcification For this reason it is better to get fresh tissue preparations *by careful dissec*tion of the temporal bone In guinea pigs, rats and cats it is possible to obtain suitable preparations from the spiral ligament with the stria vascularis, the osseous spiral lamina with the organ of Corti attached to it, the maculae, the cristae and every other part of the membranous labyrinth as well as the labyrinthine artery with its branches These preparations were dried *in vacuo* and exposed to formaldehyde vapor (Fig 1)

The histochemical reaction is considerably reinforced when the animal is given nialamide 6 hours prior to sacrificing it Nialamide inhibits monoamine oxidase and therefore causes an accumulation of catecholamines in adrenergic nerves After depletion of the tissue monoamine stores by reserpine, no fluorescence is present, proving the specificity of the reaction (Falck, 1962, Dahlstrom & Fuxe, 1964) It is also possible to differentiate between noradrenaline and dopamine in nerve endings by the administration of α-methyl-*m*-tyrosine (Falck, 1962) This substance produces a long-term depletion of noradrenaline whereas dopamine is only affected to a lesser degree over a short time

RESULTS AND DISCUSSION

A very extensive network of green fluorescent adrenergic nerve fibres is found around the basilar artery going over to the inferior anterior cerebellar artery and the labyrinthine artery with its greater branches (Fig 2 *a*) This perivascular network disappears already at the level of

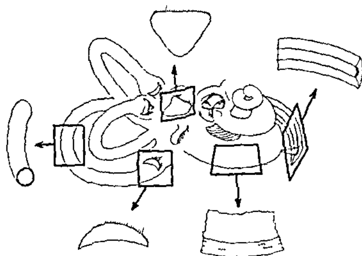


Fig 1 Schematic representation of the dissection of the labyrinth in order to obtain fresh tissue preparations of various parts of the membranous labyrinth

the modiolar branches of the cochlear artery Further peripheral nor adrenergic fibres are found with the blood vessels The perivascular plexus shows the characteristic shape and arrangement of the adrenergic nerve fibres Their course is very irregular with numerous ramifications and typical varicosities showing especially intense fluorescence The varicosities are most probably the places where transmitter is released to influence the effector cells

There are considerable differences in those perivascular plexus among different animals Whereas they are very marked in guinea pigs and rats they appear less pronounced in cats The more peripheral the less such quantitative differences are evident In spite of the relatively poor fluorescence around the inferior anterior cerebellar artery in cats there are large bundles of unmyelinated nerve fibres of various calibers in the adventitia of those vessels as revealed by the electron microscope

Within the spiral ligament and the stria vascularis in all turns we were never able to demonstrate adrenergic fibres (Fig 2 *b*) This is also consistant with the electron microscopic observations where no nervous structures are found in the spiral ligament or in the stria Sometimes however, some yellow granules can be seen in such preparations within the tissue of the spiral ligament without any connection to nerve fibres (Fig 2 *b*) We have not yet determined which substance produces this fluorescence It certainly however is not noradrenaline which on the basis of fluorescence colour could be excluded by both filter combinations Hilding (1965) described in an electron microscopic study electron dense granules in the spiral ligament which he interpreted as containing noradrenaline on the basis of a histochemical reaction described by Wood & Barrnett (1964)

Further experiments will be needed to elucidate the nature of the fluorescent substance in those granules. A direct nervous influence on the stria appears to be excluded. If and how it can be influenced on a humoral way is still unknown.

In contrast to the findings of Andrejzewski (1955) we never observed adrenergic nerve fibres in the wall of the utricle or the semicircular canals (Fig. 3 *a*), which again is in accordance with the electron microscopic findings where nerve fibres are completely lacking in the membranous wall of the labyrinth.

In the macula utriculi and in the cristae of guinea pigs green fluorescent nerve fibres indicating the presence of a primary catecholamine (noradrenaline) are, however, evident. They run independently of the blood vessels together with the other nerve fibres. (Fig. 3 *b*). They might correspond to unmyelinated nerve fibres of 0.2 to 0.5 micron thickness as regularly observed in the electron microscope between the larger myelinated vestibular fibres. The final destination of those small unmyelinated fibres has, however, not yet been established. In electron microscopic preparations they can sometimes be seen to penetrate into the sensory epithelium.

The most striking adrenergic nerve plexus is found within the osseous spiral lamina in its peripheral zone, just before the habenula perforata. A great number of green fluorescent fibres with varicosities run between the other fibres of the cochlear nerve radially, independent of the blood vessels. At the level of the habenula perforata they form a terminal plexus with continuous arcades (Fig. 4 *a*). It is difficult to follow them towards the modiolus backwards because they are hidden behind the bony shelfs of the osseous spiral lamina. This is mainly true for the basal turn where the bone is fairly thick and masks all other structures with its own unspecific fluorescence. For this reason we are only able to get good views of the most peripheral part of this adrenergic nervous plexus with the exception of the apical turn where the bone of the osseous spiral lamina is very thin and the fluorescent nerve fibres can be followed from the center of the modiolus to the habenula perforata (Fig. 4 *b*). The adrenergic fibres appear here very thin with a number of varicosities along their course. More basalwards in the cochlea the caliber of the fibres increases. They are usually best demonstrated within the second turn where the terminal plexus with its arcades is especially clear. Whether those fibres sometimes penetrate the habenula cannot yet be decided, but they never appear to cross the tunnel of Corti to reach the outer hair cells. Most likely the great majority of them turns before entering the habenula to form the arcades of the terminal plexus.

10 mg/kg reserpine i.p. (guinea pig) led to a complete disappearance of the specific fluorescence in all investigated tissues. After 400 mg/kg α-methyl-m-tyrosine i.p. (rat and guinea pig) 24 hours before sacrificing the animal, no fluorescence was seen either in the vascular plexus or in the cochlea or maculae. This made it very likely that the demonstrated



Fig. 2 a Labyrinthine artery of a guinea pig with an extensive network of adrenergic nerve fibres which appear in a green fluorescence indicating the presence of catecholamines ×600. b View of stria vascularis and part of the spiral ligament of a guinea pig. There are no adrenergic nerve fibres around or between the blood vessels. The small diffusely distributed granules appear in a yellow fluorescence which is not due to the presence of noradrenaline ×600

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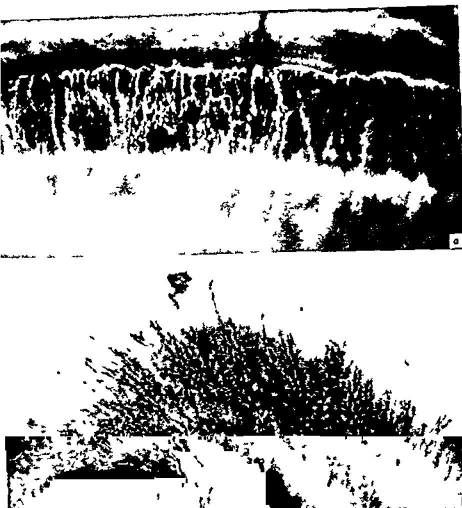


FIG 4 (*a*) View of the peripheral part of the osseous spiral lamina and the organ of Corti of the upper basal turn in a cat An extensive green fluorescent terminal plexus is seen in the area of the habenula perforata The fibres do not reach the sensory cells The three rows of outer hair cells are visible in the upper right corner ×600 (*b*) View of the osseous spiral lamina of the apical turn near the helicotrema in a cat Note the numerous adrenergic nerve fibres running radially from the modiolus to the periphery ×600

of innervation is also in accordance with the capillary nature of those vessels having no muscle cells as possible effector cells of an adrenergic innervation

In electron microscopic preparations of this area we find a number of non myelinated nerve fibres between the majority of myelinated fibres of the cochlear neurons Unmyelinated fibres in nerve trunks are usually considered to belong to the autonomic nervous system Although we do

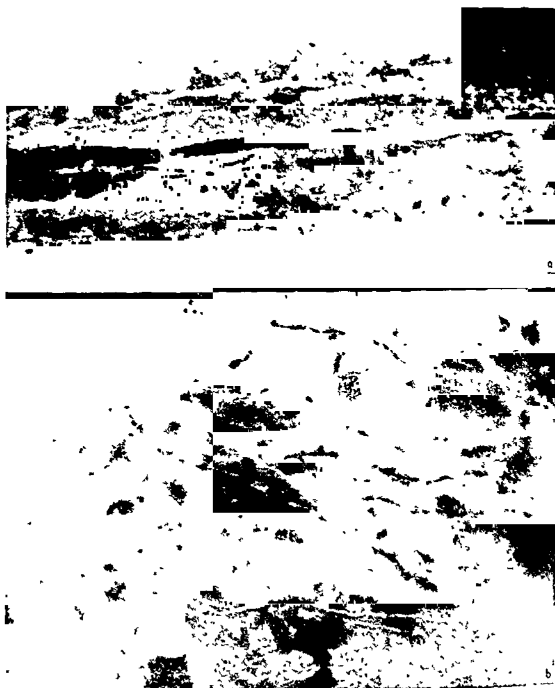
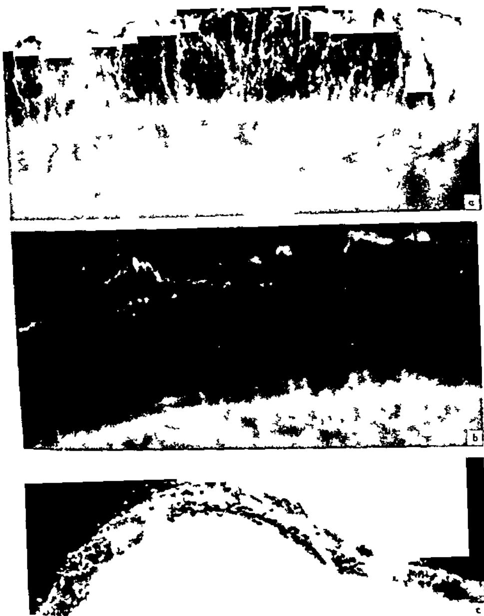


FIG. 3 (*a*) Part of a membranous semicircular canal showing no adrenergic innervation ×600 (*b*) View of part of a macula utriculi in a guinea pig Adrenergic nerve fibres with their typical varicosities are clearly seen independent of the blood vessels ×1500

fluorescence in the cochlea and macula is due to noradrenaline and not to dopamine Adrenaline could be excluded to be mainly responsible for the observed fluorescence by the time conditions of the reaction As in the spiral ligament and stria, the vessels of the osseous spiral lamina show no innervation, which is clearly seen in EM preparations This lack



F[illegible] a–c Preparations of a cat where the cochlear nerve has been transected selectively one [illegible] three weeks previously (a) Osseous spiral lamina of the second turn of the normal side the usual adrenergic terminal plexus is present ×600 (b) Osseous spiral lamina of the second turn of the operated side no adrenergic nerve fibres are visible ×600 (c) Branch of the labyrinthine artery of the operated side The perivascular adrenergic network is still present ×600

not yet have direct proof, it is likely that those unmyelinated fibres within the lamina spiralis ossea correspond mainly to the adrenergic fibres demonstrated by the histochemical fluorescence reaction Further evidence can be obtained from the observation of sac-like enlargements of such unmyelinated fibres containing dense granules of the same type as found in known adrenergic nerve plexuses or even in the adrenal medulla

In order to get information about the origin of the adrenergic innervation of the cochlea we produced different nerve lesions within the internal acoustic meatus In 10 cats we sectioned on one side either the cochlear or vestibular nerve selectively or the entire VIII nerve without damaging the labyrinthine artery After two to eight weeks the animals were sacrificed and their cochleae examined Nialamide was given (200 mg/kg i p) 6 hours prior to the death of the animal in order to reinforce the fluorescence In this way the chance of overlooking weakly fluorescent fibres was minimalized

After selective lesions of the vestibular nerve, which includes the section of the olivo-cochlear bundle, there was no considerable difference between the adrenergic nerve plexus of the cochlea of the operated and the unoperated side Transection of the cochlear nerve or the entire VIII nerve, however, resulted in disappearance of at least nearly total reduction of the adrenergic nerve plexus on the operated side (Fig 5 *a, b*) The few remaining fibres appeared frequently swollen with unusually large varicosities, as also mentioned by Fuxe (1964) for degenerating fibres The perivascular plexus around the branches of the labyrinthine artery was still present (Fig 5 *c*)

Thus we can conclude that the adrenergic nerve plexus within the osseous spiral lamina originates at least for its greatest part from the central nervous system reaching the periphery with the cochlear nerve

Therefore we find two different systems of adrenergic innervation of the inner ear The first, which has earlier been postulated and partly demonstrated is the perivascular system It is very dense in the main arterial branches of the inner ear but disappears already in the periphery of the modiolus The second, much more impressive system, consists of fibres extending between the regular cochlear nerve fibres The fibres of this system are independent of the blood vessels originate in the central nervous system and form a peripheral plexus in the area of the habenula perforata (Fig 6 *a*)

The functional significance of this adrenergic innervation of the cochlea is still unknown A direct effect of sympathetic stimulation on the threshold of a sensory receptor could be demonstrated by Loewenstein in touch receptors We might be justified to assume a similar regulative role for this second adrenergic system of the inner ear which is independent of the blood vessels This, however has not yet been directly demonstrated

The localization of this adrenergic terminal plexus just before the habenula perforata needs further consideration This is exactly the area

that the adrenergic terminal plexus which lies exactly in this area influences the formation of action potentials for instance by lowering or increasing their threshold (Fig 6 *b*)

The mechanism of the formation of action potentials has been thoroughly studied in the motor neurons (Eccles 1964) If there is a depolarization and fall of the potential at the initial segment to a critical value, an action potential spike originates according to an all or none law The depolarization is due to a graded generator potential The threshold for the formation and take off of an action potential can be influenced from outside When the threshold is lowered a smaller generator potential is sufficient to trigger off the formation of such an all or non-spike of the action potential and vice versa

In accordance with the situation in the motor neurons, the adrenergic nervous plexus in the osseous spiral lamina could influence the threshold of the initial segments of the cochlear neurons by releasing noradrenaline which is known to be a transmitter in peripheral nerves The diffuse distribution of the terminal adrenergic plexus makes it more likely that this system exerts a general control of the sensitivity of the sensory organ rather than being involved in localized discriminative mechanisms of the cochlea

ZUSAMMENFASSUNG

Mit dem direkten histochemischen Nachweis von Noradrenalin nach der Methode von Falck und Hillarp kann die adrenergische Innervation des Labyrinthes erstmals eindeutig und selektiv dargestellt werden Zwei verschiedene adrenergische Innervationssysteme gelangen ins Innenohr 1 Ein reiches perivasculäres Nervengeflecht das sich von der Arteria basilaris kommend bis in die grossen Äste der Arteria labyrinthica erstreckt 2 Ein ausgedehntes adrenergisches Innervationsnetz in der Lamina spiralis ossea und unterhalb der vestibulären Sinnesepithelien unabhängig von Blutgefässen Es bildet einen dichten Terminalplexus in der Gegend der Habenula perforata Mit selektiver Durchtrennung des Nervus vestibularis cochlearis oder des ganzen VIII Nerven konnte gezeigt werden dass diese adrenergischen Fasern aus dem Zentralnervensystem kommen und die Peripherie zusammen mit dem Nervus cochlearis erreichen Es wird eine mögliche Interpretation ihrer funktionellen Bedeutung diskutiert

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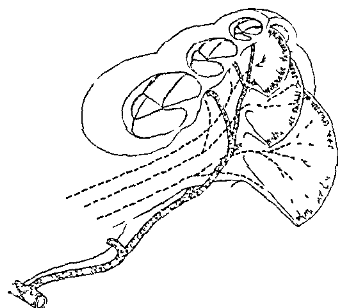
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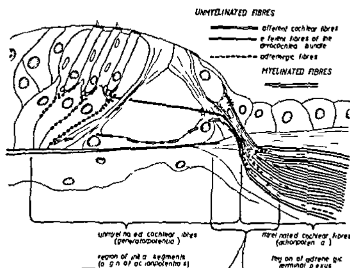
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FIG. 6. (*a*) Schematic representation of the double adrenergic innervation of the cochlea by two different systems: (1) the perivascular system which belongs to the peripheral post ganglionic sympathetic system. (2) An adrenergic innervation system independent of the blood vessels originating in the central nervous system and reaching the periphery with the cochlear nerve. It is represented with interrupted lines. (*b*) Schematic representation of the organ of Corti indicating the three different types of its innervation. The adrenergic terminal plexus is located in the region of the initial segments of the cochlear neurons where presumably the afferent action potentials originate.

where the action potentials of the cochlear nerve are thought to take their origin. The afferent unmyelinated fibres of the cochlear neurons begin to get their myelin sheaths at this level. According to the present concept the first node of Ranvier or the beginning of the myelin sheath represents the so-called initial segment where the action potentials take their origin and saltatory conduction of nerve impulses starts. It is inviting to speculate

UNTERSUCHUNGEN ÜBER DIE URSACHE DER SPEZIFISCH OTOTOXISCHEN WIRKUNG DER BASISCHEN STREPTOMYCES-ANTIBIOTIKA UNTER BESONDERER BERÜCKSICHTIGUNG DES KANAMYCINS

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Aus der Hals-, Nasen-, Ohrenklinik der Medizinischen Akademie Düsseldorf (Direktor: Prof. Dr. Meyer zum Gottesberge) und den Forschungslaboratorien der Chemie Grünenthal GmbH, Stolberg/Rhld. (Med. Leiter: Dr. Muckter)

Unsere Untersuchungen ergaben eine überraschend hohe Kanamycinkonzentration in der Peri- und vor allem auch in der Endolymphe. Sie enthielten z. B. 12 Stunden post injectionem 10mal mehr Kanamycin als das Blut und 20mal mehr als Herz und Leber. Die Tatsache, daß der Kanamycingehalt des Innenohres über 100mal so hoch ist wie im Gehirn, weist darauf hin, daß wahrscheinlich im Innenohr und nicht im ZNS der Schädigungsort zu suchen ist.

Die Anreicherung des Kanamycins erfolgte im Vergleich zum Blut im Innenohr deutlich langsamer. Insbesondere war der Abtransport des Kanamycins aus dem Innenohr erheblich verzögert. Die Halbwertzeit für Kanamycin betrug im Blut 85 Min., im Innenohr über 10 Stunden. Anreicherungsvorgang und behinderter Abtransport werden durch eine besondere Eigenschaft der ototoxischen Antibiotika erklärt: im Gegensatz zu anderen Antibiotica sind die ototoxischen nämlich nicht resorbierbar. Die hierdurch bedingte Kanamycinanhäufung und außergewöhnlich lange Einwirkungszeit im Innenohr sind u. E. für die spezifisch ototoxische Wirkung ursächlich verantwortlich.

Die Literatur über die toxische Wirkung der basischen Streptomyces-Antibiotika läßt sich, wie Muckter (1961) in seiner Monographie bemerkt, nicht mehr übersehen. Zahlreiche Befunde und experimentelle Ergebnisse wurden in den letzten Jahren mitgeteilt. Im Vordergrund standen neben klinischen Beobachtungen Arbeiten, die mit Hilfe histologischer, histochemischer und autoradiographischer Methoden durchgeführt wurden. Verschiedene Anzeichen einer Innenohrschädigung konnten so nachgewiesen werden. Es war auch möglich, eine Aussage über die Lokalisation der Schädigung zu machen (Causse, Gondet & Vallancien 1948, Graf 1951, Ruedi, Graf & Tschirren 1953, Hawkins, Wolcott & O'Shanny 1956-57, Berg 1951, Sokolowski 1952, Neumann & Neubert 1958, Musebeck &

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Schätzle, 1963). Die Frage nach der eigentlichen Ursache der Ototoxizität dieser Substanzen blieb aber bis heute unbeantwortet.

Im Rahmen unserer Studien über die Permeationsvorgänge im Innenohr und an anderen Organen fiel uns eine besondere Eigenschaft auf, die nur den ototoxisch wirkenden Antibiotika gemeinsam ist, nämlich daß sie nicht resorbierbar sind. Es ist bekannt, daß z. B. Streptomycin und Kanamycin bei oraler Zufuhr von den Mucosazellen des Darmes nicht resorbiert werden können. Während der übrige Darminhalt zum größten Teil der Resorption unterliegt, bleibt das Antibiotikum zurück und erreicht infolgedessen im Darm eine hohe Konzentration.

Ein ähnlicher Vorgang ist auch in den Nierentubuli anzunehmen. In der Niere vermochten *Stremmler & Dudlowzik* (1961), *Lagler, Osterloh & Mueller* (1959/60), *Andre* (1956) und *Mascitelli-Coriandoli, Boldrini & Citterio* (1958) histologisch, mikrobiologisch sowie auf autoradiographischem und biochemischem Wege eine elektive Anreicherung und Ablagerung von Dihydrostreptomycin, Kanamycin und Neomycin, die bekanntlich auch in den Tubuli nicht rückresorbiert werden können, in den Tubulusepithelien nachzuweisen. Die Anreicherung erklärt wahrscheinlich die spezifisch nephrotoxische Wirkung dieser Substanzen.

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Filterblättchen Nr. 22 (Schleicher & Schüll) 6 mm. Teststamm: B. subtilis ATCC 6633. (Niedrigste feststellbare Kanamycinkonzentration im Serum und Gewebe 0.01 µg/ml bzw. µg/g, in Lymphe 0.5 µg/ml.) Eine genauere Bestimmung mit Hilfe von H-markiertem Kanamycin ist in Vorbereitung.

Versuchsbedingungen

30 Meerschweinchen mit einem durchschnittlichen Gewicht von 250 Gramm erhielten 10 Tage lang täglich eine Injektion von 250 mg Kanamycinsulfat pro kg subcutan [1]. 30, 60 und 120 Minuten nach der letzten Injektion entnahmen wir den Tieren in Urethan-Äther-Narkose Perilymphe aus der Scala vestibuli und gleichzeitig Blutproben, die auf ihren Kanamycingehalt untersucht wurden.

Eine andere Serie von 30 Meerschweinchen wurde nach der gleichen Vorbehandlung, wie oben angegeben, 30, 60 und 120 Minuten nach der letzten Injektion dekapitiert. Anschließend wurden sofort die Bullen freigelegt, eröffnet und in Isopentan und flüssigem Stickstoff unter Vermeidung von Gasbildung vorsichtig eingefroren. Danach erfolgte in der Tiefkühlkammer die weitere Präparation zur Gewinnung von Perilymphe sowie der Endolymphe. Da zur Messung des Kanamycingehaltes relativ große Mengen erforderlich waren, mußten die Peri- und Endolymphen stets von 3–6 Tieren zusammengenommen und ausgewertet werden. Evtl. Blutbeimischungen ließen sich durch eine photometrische Hb-Bestimmung feststellen und berechnen.

In einer weiteren Versuchsreihe (20 Tiere) verfolgten wir nach einer 11tägigen Vorbehandlung mit täglich 250 mg Kanamycin/kg den Abtransport des Kanamycins aus den einzelnen Organen über einen längeren Zeitraum. 5 und 12 Stunden nach der letzten Injektion wurden die Tiere getötet. Außer Endo-, Perilymphe und Blut wurden auch das Herz, die Leber, das Großhirn und der Hirnstamm entnommen und auf ihren Kanamycingehalt untersucht.

ERGEBNISSE

Im Vordergrund unserer Untersuchungen stand die Frage:

1) Wieviel Kanamycin gelangt in das Innenohr?
2) Wie verhält es sich mit der Kanamycin-Clearance dieses Organes?

Das Verhalten des Kanamycins im Blut

Eine halbe Stunde nach der letzten Injektion von 250 mg Kanamycin pro kg fand sich im Blutserum eine Kanamycinkonzentration von 515 γ/ml. Dieses war der höchste Wert, den wir messen konnten. Dann folgte, wie aus der Abbildung hervorgeht, ein steiler Abfall. Eine halbe Stunde später war der Kanamycinspiegel des Blutes bereits auf 373 γ/ml gesunken. Das bedeutet eine Abnahme um 28%. Nach einer weiteren Stunde konnten wir nur noch einen Kanamycingehalt von 126 Gamma in 100 ml Blut feststellen. Mit anderen Worten, zu diesem Zeitpunkt war bereits 75% des injizierten Kanamycins aus dem Blut eliminiert. 5 Stunden nach der Injektion

[1] Wir danken der Chemie Grünenthal GmbH, die uns freundlicherweise Kanamycin und Versuchstiere zur Verfügung stellte.

Schätzle, 1963). Die Frage nach der eigentlichen Ursache der Ototoxizität dieser Substanzen blieb aber bis heute unbeantwortet.

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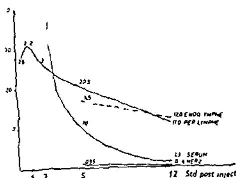


Abb. 2. Vergleich der Kanamycinkonzentrationen in Endo- und Perilymphe, in Blut und Herz

tistisch nicht sichern. Ob hier wirklich ein Unterschied besteht, mußten noch weitere Messungen mit markiertem Kanamycin klären.

Die Tatsache, daß der Kanamycinspiegel im Blut sehr schnell fiel, in der Endo- und Perilymphe dagegen auch nach zwei Stunden noch praktisch unverändert einen Maximalwert aufwies, veranlaßte uns, den Kanamycingehalt über einen längeren Zeitraum von 5 und 12 Stunden hinaus zu verfolgen.

Fünf Stunden nach der letzten Injektion konnten wir im Blut nicht mehr als 10 γ/ml feststellen. Die Perilymphe enthielt zu diesem Zeitpunkt mit 20 γ/ml doppelt soviel Kanamycin wie das Blut.

Zwölf Stunden später zeigte sich ein noch deutlicheres Überwiegen der Kanamycinkonzentration der Innenohrflüssigkeiten im Vergleich zum Blut. Während der Blutspiegel schon auf einen Wert von ungefähr 1 γ/ml abgefallen war, fanden sich in der Perilymphe immer noch 11 γ/ml. Die Endolymphe enthielt sogar mit 12 γ/ml annähernd 12mal soviel Kanamycin wie das Blut.

Vergleich der Kanamycinkonzentration im Innenohr mit der anderer Organe

Wie extrem hoch der Kanamycingehalt der Innenohrflüssigkeiten in Wirklichkeit ist, kommt besonders deutlich bei einem Vergleich mit anderen Organen, wie Herz, Leber, Großhirn und Hirnstamm, zum Ausdruck (Abb. 3). Im Herz fanden sich 5 Stunden nach der letzten Kanamycingabe nur 0,05 γ, in der Leber 0,76 γ und im Großhirn und Hirnstamm sogar nur 0,16 γ bzw. 0,15 γ/g. Das bedeutet, die Perilymphe enthielt, verglichen mit dem Herz, 20mal soviel und verglichen mit der Leber mehr als 25mal soviel Kanamycin. Besonderes Interesse verdient der erhebliche Unterschied zwischen der Perilymphe und dem ZNS hinsichtlich ihres Kanamycingehaltes. In der Perilymphe konnten wir 125mal mehr Kanamycin als im Großhirn und im Hirnstamm feststellen. Ähnliche Werte ergeben sich bei einem

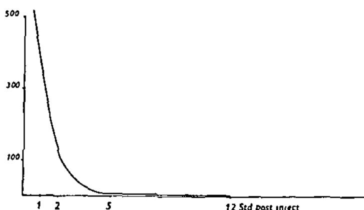


Abb 1 Kanamycinspiegel des Blutes nach intraperitonealer Injection von Kanamycin Sulfat

ließen sich nicht mehr als 10 γ/ml und nach insgesamt 12 Stunden nur noch 1 Gamma Kanamycin/ml Serum nachweisen Hieraus ergibt sich eine Halbwertzeit fur Kanamycin im Blut von ungefähr 85 Minuten (Abb 1)

Die Kanamycinkonzentration in Endo- und Perilymphe

Im Gegensatz zu den bisherigen Vorstellungen fand sich auch in der Perilymphe bereits eine halbe Stunde nach der letzten Injektion eine relativ hohe Kanamycinkonzentration von 28 γ/ml Während der Kanamycinspiegel im Blut zu diesem Zeitpunkt schon seinen Höchstwert erreicht hatte, stieg der Kanamycingehalt des Innenohres im weiteren Verlauf noch an Er erreichte erst nach einer Stunde sein Maximum mit 31 γ/ml Aber auch nach 2 Stunden konnten wir noch 27 γ Kanamycin in einem ml Perilymphe messen (Abb 2) Diese Tatsache ist um so bemerkenswerter, da die Blutserumkonzentration im gleichen Zeitraum von zunachst 515 γ/ml, 30 Minuten post injectionem, bereits nach weiteren 30 Minuten um 28% und 60 Minuten später um 75% gefallen war Wahrend die Kanamycinkonzentration im Blut 30 Minuten post injectionem 18mal so hoch lag wie in der Perilymphe, war sie nach einer Stunde post injectionem nur noch um das 12fache erhoht Nach insgesamt zwei Stunden hatte sich das Verhältnis weiter zugunsten der Perilymphe verschoben Das Blutserum enthielt jetzt nur noch knapp 4mal soviel Kanamycin

Die mit der Gefriertechnik gewonnenen Werte zeigten mit den in vivo erhaltenen Ergebnissen eine weitgehende Übereinstimmung Mit Hilfe der Gefriermethode war es außerdem möglich, auch die Endolymphe auf ihren Kanamycingehalt zu untersuchen Die Kanamycinkonzentration der Endolymphe betrug nach 2 Stunden 24,5 γ/ml, die der Perilymphe bei der gleichen Technik 20,5 γ/ml Der Kanamycinspiegel im Blut war zu diesem Zeitpunkt mit 126 γ/ml noch 6mal so hoch wie in der Perilymphe und 5mal höher als in der Endolymphe Die scheinbar hohere Kanamycinkonzentration in der Endolymphe im Vergleich zur Perilymphe ließ sich sta-

DISKUSSION

Wie wir bereits in der Einleitung erwähnten brachte uns die schlechte Resorbierbarkeit und die hierdurch hervorgerufene Anreicherung der Streptomyces Antibiotika nicht nur in der Niere sondern ebenso bei enteraler Gabe im Darm auf den Gedanken daß möglicherweise auch im Innenohr wo ebenfalls Resorptionsvorgänge angenommen werden höhere Konzentrationen auftreten Wir hofften auf diese Weise eine Erklärung für den spezifisch ototoxischen Wirkungsmechanismus im Innenohr zu erhalten

Die Untersuchungen bestätigten unseren Verdacht, daß es im Innenohr zu einer Anreicherung des Kanamycins kommt Die gemessesen hohen Konzentrationen überraschten insbesondere im Hinblick auf die bislang vorherrschende Annahme daß Kanamycin die Blut Liquor Schranke nicht zu passieren vermag Man schloß hieraus daß wahrscheinlich auch im Innenohr keine wesentlichen Kanamycinmengen auftreten

Der Verlauf der Anreicherung des Kanamycins und seines Abtransportes aus dem Innenohr verdient besondere Beachtung Die Anreicherung dieser Substanz erfolgte im Vergleich zum Blut in den Innenohrflüssigkeiten nur langsam Nach einer Stunde erreichte die Kanamycinkonzentration im Innenohr ihr Maximum Bemerkenswert ist daß der Anstieg trotz gleichzeitiger Abnahme der Blutkonzentration stattfand

Noch deutlicher war der Abtransport des Kanamycins aus dem Innenohr verzögert Der Blutspiegel des Kanamycins hatte bereits nach einer halben Stunde sein Maximum überschritten und war nach einer Stunde stark gefallen Die Halbwertzeit des Kanamycins im Blut beträgt nach unseren Messungen schätzungsweise 80 Minuten Ähnliche Zeiten werden in der Literatur für Streptomycin angegeben SOUS (Muckter 1961) fand beim Kaninchen eine Halbwertzeit für Dihydro Streptomycin von 80 Minuten und Dost (1953) beim Menschen von 72 Minuten Dagegen konnten wir im Innenohr eine wesentlich längere Halbwertzeit für Kanamycin von annähernd 10 Stunden feststellen Aber auch nach 12 Stunden fand sich in den Innenohrflüssigkeiten mit 12 ml noch fast die Hälfte des Kanamycins wieder Die Kanamycinkonzentration im Innenohr war zu diesem Zeitpunkt 10mal so hoch wie im Blut das nur noch etwas mehr als 1 γ Kanamycin/ml aufwies

Das entgegengesetzte Verhalten der Kanamycinkonzentration im Blut und in den Innenohrflüssigkeiten scheint uns ein Hinweis zu sein daß im Innenohr offenbar ein besonderer Anreicherungsprozeß vor sich geht Vorstellbar wäre zum Beispiel daß zunächst nur wenig Kanamycin — sei es mit der Peri oder Endolymphe — das Innenohr erreicht Während die übrige Flüssigkeit mit ihren gelösten Bestandteilen vor allem den Elektrolyten dem normalen Austauschvorgang unterliegt und wieder resorbiert wird scheint dieser Weg für Kanamycin das sehr schwer resorbierbar ist nicht möglich zu sein Kanamycin bleibt infolgedessen im Innenohr zurück und beginnt sich hier langsam anzuhäufen Es hat den Anschein als

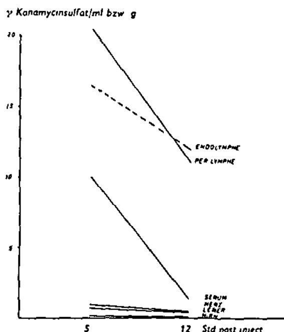


Abb 3 Vergleich der Kanamycinkonzentrationen in Endo- und Perilymphe, in Blut Herz Leber und Gehirn

Vergleich mit der Endolymphe. Dies ist um so bemerkenswerter, da in früheren Arbeiten (Escher, 1949, Floberg, Hamberger & Hyden, 1949, Winston *et al*, 1948, Christensen *et al*, 1950; de Kleyn & van Deinse, 1950, Secondi, 1954 und Riskaer *et al*, 1956) die primäre Noxe durch Streptomycein im cochleovestibulären Kerngebiet angenommen wurde Unser Beitrag liefert eine weitere Stütze zu den histologischen Untersuchungen (Causse, Gondet & Vallancien, 1948, Berg, 1951, Graf, 1951, Ruedi *et al*, 1952, Catalano & Madonia, 1956, Hawkins *et al*, 1956–57, Neumann & Neubert, 1958) und elektrophysiologischen Befunden (Davis *et al*, 1958), die auf eine Primärschädigung im peripheren Hör- und Gleichgewichtsorgan hinweisen

Nach insgesamt 12 Stunden post injectionem konnten wir, wie die nachstehende Aufstellung zeigt, in der Leber, im Herz, Großhirn und Hirnstamm nur noch annähernd die Hälfte des Kanamycins feststellen, wie 7 Stunden zuvor

Obwohl durch die vielfach höhere Kanamycinkonzentration im Innenohr ein günstigeres Diffusionsgefälle gegeben war, verlief der Abtransport des Kanamycins im Vergleich mit anderen Organen nicht schneller, sondern eher verzögert

Stunden post inj	Herz	Leber	Großhirn	Hirn stamm	Peri lymphe	Endo lymphe	
5	0,95	0,76	0,16	0,15	20,3	16,5	γ Kanamycin g
12	0,47	0,42	0,09	0,10	11,0	12,0	γ Kanamycin g

Der etwas höhere Kanamycingehalt im Herz und in der Leber im Gegensatz zum ZNS geht sicher zum größten Teil auf den hohen Blutgehalt dieser Organe zurück

Linie als Schädigungsort anzusehen ist Diese Annahme wird auch durch die Mehrzahl aller histologischen und histochemischen Befunde bestätigt Für die Auffassung einer zentralen Schädigung, vor allem im Bereich der Kerngebiete, ergaben sich bei unseren Untersuchungen keine Hinweise Die Konzentration des Kanamycins ist in diesem Hirnbereich so gering und unterscheidet sich nicht von anderen Hirnregionen, daß wir eine zentrale Giftwirkung nicht für wahrscheinlich halten möchten Interessant sind in diesem Zusammenhang Befunde von André (1961), die mit tritiummarkiertem Dihydro-Streptomycin erhoben wurden Auch Streptomycin konnte von André im ZNS nur in sehr geringen Konzentrationen nachgewiesen werden

Ausführlichere und noch genauere Untersuchungen sind mit markiertem Kanamycin vorgesehen Uns interessiert im besonderen, ob eine 10tägige Kanamycinvorbehandlung (klinisch gleichbedeutend mit vollständiger Ertaubung) notwendig ist, um die Kanamycin Clearance im Innenohr so augenfällig herabzusetzen, oder ob schon die ersten Injektionen eine starke Anreicherung im Innenohr bewirken Wir hoffen außerdem mit Hilfe des markierten Kanamycins weitere Aufschlüsse und Einzelheiten über den toxikologischen Wirkungsmechanismus, insbesondere auch hinsichtlich der Lokalisation des Kanamycins in den verschiedenen Cochleaabschnitten zu erhalten

SUMMARY

Our experiments reveal a surprisingly high concentration of Kanamycin in perilymphatic and especially in endolymphatic fluids Their content of Kanamycin 12 hours after injection was for example 10 times higher than in the blood and 20 times higher than that of the heart and liver tissue The concentration of Kanamycin in the inner ear exceeds that of the brain more than 100 times From this we conclude that the toxic injury occurs in the labyrinth and not in the CNS

The elimination of Kanamycin from the inner ear was extremely delayed The half life time for Kanamycin in the blood was found to be only 85 minutes in the perilymph about 10 hours The accumulation and retarded elimination of Kanamycin can be explained by a special criterion which is specific for the ototoxic antibiotics they cannot be absorbed The high concentration *together with the* prolonged availability of Kanamycin in the inner ear are responsible for the ototoxic effect

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ginge diese Anreicherung im Sinne eines Klärmechanismus vonstatten. Das Innenohr und seine Membranen würden in dieser Vorstellung die Funktion eines biologischen Filters einnehmen. Noch größere Schwierigkeiten bereitet offenbar die Entfernung des Kanamycins aus dem Innenohr. Der erheblich verzögerte Abtransport spricht ebenfalls für die Annahme, daß wahrscheinlich die Resorption erschwert ist.

Ein ähnlicher Weg der Anreicherung des Kanamycins ist, wie bereits erwähnt wurde, vom Darm her bekannt.

Der gleiche Prozeß kann auf Grund der Befunde, die an den Tubuluszellen erhoben wurden (Staemmler, 1957, Staemmler & Dudkovik, 1960, Lagler, Osterloh & Muckter, 1959–60, Mascitelli-Coriandoli, Boldrini & Citterio, 1958, 1959), auch in den Nierentubuli angenommen werden. In ausführlichen Untersuchungen konnten erstaunlich enge funktionelle Beziehungen zwischen den Resorptionsvorgängen an Tubulus- und Darmepithelien, die ebenso elektronenmikroskopisch in ihrer polaren Struktur eine große Ähnlichkeit besitzen, nachgewiesen werden (Stupp, 1960, Rummel & Stupp, 1962). Aber auch die Epithelien der Tubuli und der Stria vascularis weisen, wie Rauch (1961) zeigen konnte, morphologische und funktionelle Beziehungen auf.

Unsere Kanamycinbefunde stellen einen weiteren Hinweis dar, daß offenbar Analogien *zwischen den Zellen mit resorptiver Eigenschaft* bestehen und geben eine Antwort auf die in der Literatur immer wieder gestellte Frage nach der Beziehung zwischen oto- und nephrotoxischer Wirkung dieser Antibiotika. Sie scheinen die Auffassung von Rauch, wonach die Stria vascularis eine resorptive Funktion besitzt, zu bestätigen. Möglicherweise ist die Stria vascularis für die lokale Kanamycinanreicherung im Innenohr ursächlich verantwortlich. Auch die erstaunlich lange Verweildauer des Kanamycins und der verzögerte Abtransport aus dem Innenohr ließen sich *durch eine erschwerte Resorption* zwanglos erklären.

Mit der hohen Konzentration und langen Einwirkungszeit des Kanamycins im Innenohr sind alle Voraussetzungen für eine spezifisch ototoxische Wirkung erfüllt. Wir glauben, aufgrund der vorliegenden Befunde annehmen zu können, daß das Innenohr wahrscheinlich nicht empfindlicher gegen die Giftwirkung des Kanamycins ist als andere Organe, z. B. das Auge und insbesondere das Nervensystem. Das Schicksal des Innenohres ist u. E. in der Tatsache zu suchen, daß dieses Sinnesorgan mehr als jedes andere einer *extrem hohen Giftkonzentration über eine lange Zeit* ausgesetzt ist. Damit deutet sich eine überraschend einfache Lösung für ein Problem an, das seit Jahren das Interesse und die Aufmerksamkeit zahlreicher Untersucher in Anspruch genommen hat. Vermutungen, die von einer besonderen Sensibilität des Innenohres gegenüber den Streptomycesgiften ausgehen, und Vorstellungen von einer besonderen Affinität dieser Substanzen zum Innenohr — Hypothesen, von denen immer wieder in der Literatur die Rede ist — finden so ihre Erklärung.

Unsere Befunde weisen ferner darauf hin, daß das Innenohr in erster

RADIOLOGICAL EXAMINATION OF THE INNER EAR OF DEAF-MUTES PRESENTING THE CERVICO-OCULO-ACUSTICUS SYNDROME

With a Summary of Roentgenological and Pathologico-Anatomical Findings in Other Endogenous Forms of Deafness

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In three congenitally deaf females presenting the "cervico oculo acusticus syndrome" (perceptive deafness associated with fused neck vertebrae and spina bifida occulta [Klippel Feil anomaly] and abducens palsy) the bony labyrinth (cochlea and vestibular apparatus) appeared to be underdeveloped as stated by X-ray examination Only in one case, at one side, where the labyrinth seemed to be least underdeveloped, a normal vestibular function was found These findings support the opinion that the syndrome represents an entity different from the other forms of endogenous deafness The authors give a summary of the roentgenological and pathologico-anatomical findings from the literature in other forms of endogenous deafness

INTRODUCTION

A deaf person is of course examined otologically, including the making of an audiogram and—in most cases—examining the vestibular function Radiological examination and—if possible—pathologico-anatomical investigations however, are of much value for a better knowledge of the causes of deafness If we confine ourselves to endogenous congenital deafness, we can state that we know already something about the anomalies in the inner ear

In the most common form of *congenital recessively inherited deafness* (type Scheibe) the nervous part of the auditory organ and/or the organ of Corti are damaged but the bony labyrinth, including the semicircular canals is formed normally in most cases (Secretan, 1954, Guli & Bonetti 1956 Ormerod 1958 and 1960, Altmann, 1950 and 1964) Altmann (1963) states that in some cases the semicircular canals, especially the lateral ones, are affected (anatomico-pathologically investigated) According to Arnvig (1955) in 13% of the cases there is no vestibular response, in 21% abnormal response This statement agrees with the conclusions of most other

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only by Fisch (1959) and Thorkilgaard (1962). The organ of Corti was fully absent. The bony vestibular organs and the cochlea were normal. In the latter the caloric response was normal at both sides, the cochlea, vestibular ducts and the internal meatus were normal.

Two brothers presenting a syndrome of *perceptive deafness associated with split-hand and split foot* (Wildervanck, 1963 *b*) were examined radiologically by Dr C. C. Derks (data unpublished). In the elder boy no aberrations on mastoid roentgenograms nor on Towne-Twining views were seen. Planigraphy of the temporal bones revealed a fully normal picture of aditus, labyrinth, vestibulum, canals, cochlea and meatus acusticus internus. In the younger boy were found normal pneumatisation in Stenvers' and Schuler views. The semicircular canals were present as well as the cochlea and the meatus acusticus internus. Towne-Twining views confirmed these findings. Planigraphy of the temporal bones revealed normal meatus acusticus internus, cochlea, vestibulum and canals. Ossicles were present.

Now we come to the syndrome mentioned in the title, the *cervico oculo-acusticus syndrome* (Wildervanck, 1952, 1960 *a*, *b*, 1961, 1963 *a*, 1964, Pintucci & Di Tizio 1961, Grimaud *et al.*, 1962, Waardenburg, 1963, Leiber & Olbrich, 1963, Fraser 1964, Whetnall & Fry, 1964) consisting of perceptive deafness, concretion of neck vertebrae, sometimes also of the upper thoracic vertebrae with spina bifida occulta (Klippel-Feil anomaly), and abducens palsy with retractio bulbi of one or both eyes, i.e. an inward retraction of the eye bulb when looking with the affected eye in the direction of the nose. One of these symptoms may be lacking (as is the case in many syndromes). Among the relatives of many patients there were found more 'short necks', anencephaly, rachischisis (spina bifida aperta), hydrocephalus, all anomalies belonging to the so-called "status dysraphicus" (caused by incomplete closure of the neural plate) and deafness most probably having a common factorial background. The mode of heredity is not very clear, polyfactorial inheritance is most likely. 51 *cases are known* up to now, only 4 of them being males. The frequency of deaf children with the syndrome among all deaf children may be estimated to be about 1%. Taking into account only the boys the incidence is only a fraction of a per cent. The first case examined radiologically concerns a boy (♂) and has been published by Franceschetti & Klein (1954). There existed total deafness *at the left* side and hardness of hearing at the right side. Vestibular reactions were not performed. The boy showed left facial hypoplasia with defective implantation of the teeth, auricular appendages at the left side and the Klippel Feil anomaly with torticollis. Moreover he displayed a left subconjunctival lipoma, a slight heterochromia iridum, and complete *abolition* of abduction and restriction of adduction of both eyes, the latter accompanied by a retraction of the globe. The family history revealed two deaf sibs, a *deaf uncle* and an uncle with club-feet. *Radiological examination* revealed a fully normal picture at the right side,

investigators (Grimaud *et al*, 1962) Lindenov (1945) found also a great preponderance of normal vestibular function in hereditary cases According to Hanhart (1962) in 25% of the patients abnormal or failing reactions are present

In the rare *hereditary labyrinthic progressive form of deafness*, in most cases non-congenital, inherited in a dominant way of transmission (type Mondini), the bony labyrinth is severely deformed and in most cases the vestibular function is affected (Grimaud *et al*, *l c*)

In *unilateral deafness*, extensively studied by Everberg (1960 *a*, *b*, *c* 1961, 1962, 1963) X-ray investigations with Massiot's polytome in 18% revealed abnormal labyrinthic appearances at the deaf side, the semicircular canals were partially or fully obliterated Some of these cases were *endogenous*, congenital cases; 25% of them follow an irregular dominant way of transmission, but presumably this form of deafness is not a real *genetic entity* (*Everberg, 1960 c*). *Everberg (1960 a) stresses the fact that* not in all cases where the vestibular reactions were diminished or even absent, X-ray tomographs show *abnormalities* Everberg, Ratjen & Sörensen (1963 *b*) examined radiologically another case of unilateral deafness in which the acoustic and vestibular functions were absent

Tomographs, however, revealed a normal middle ear, semicircular canals, vestibulum and cochlea, but an osseous atresia of the narrowed auditory meatus was found The authors remark that obliteration of semicircular canals has previously been assumed to be due exclusively to the sequelae of suppurative labyrinthitis, otogenic or meningogenic They are right however, when they state that it is beyond doubt that these labyrinthic anomalies may also be congenital *Altmann (1953) stated that severe malformations of the semicircular canals have, as a rule, been observed only in cases of atresia auris congenita* Everberg *et al* made clear that there are exceptions to this rule

As early as 1907 Siebenmann & Bing investigated pathologico-anatomically a case of *Usher's syndrome* (deafness with retinitis pigmentosa), recessively inherited The bony labyrinth appeared to be normal though the semicircular canals are not mentioned particularly

The ear of one patient suffering from *deafness and electrocardiographic abnormalities* probably a genetic entity, could be examined post *mortem* by Fraser, Froggatt & James (1964) No alterations of the bony labyrinth were *found*

After Fraser (1965) in cases of *Pendred's syndrome* (deafness with goitre) skull rays show a normal architecture of the middle and inner ear Vestibular response may be diminished or normal

Two cases of *Waardenburg's syndrome* consisting of lateral displacement of the medial canthi and lacrimal points a hyperplastic broad nasal root, hyperplasia of the medial portions of the eyebrows heterochromia iridum, congenital deafness and circumscribed *albinism of the frontal head* hair, dominantly inherited have been investigated histologically until now

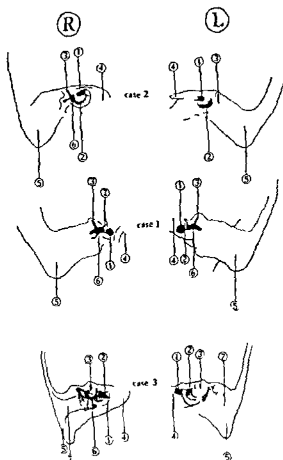


FIG 1 Schematic drawings after the X ray tomograms of the three cases mentioned in the paper *Upper row* tomograms of the petrosa in Stenvers projection (case 2) *Middle row* tomograms of the petrosa in Stenvers projection of case 1 *Lower row* tomograms in transorbital projection of case 3

In all cases there is evidence of the existence of cochlear and vestibular structures We have the impression that in case 2 the internal meati acustici are somewhat constricted and that in cases 2 and 3 structures of the inner ear are underdeveloped especially on the left side With regard to the quality of the X ray pictures, obtained by linear tomography we must refrain however from further anatomico-diagnostic interpretations *1* Meatus acusticus internus *2* cochlea *3* superior semicircular canal *4* apex pyramids *5* mastoid *6* vestibulum *7* meatus acusticus externus

presents abducens palsy at the left side with retractio bulbi The left eye fissure is narrowed In the family more congenitally deaf members occur a father's brother a cousin of the mother and a paternal cousin of the third degree Another brother of the father shows heterochromia iridum The parents are not consanguineous Our present examination revealed the following features *Hearing* at both sides completely deaf Eardrums normal, manubrium mallei distinct *Caloric examination* at both sides no

a the left side the labyrinth was coarse and the superior semicircular canal was absent. Though this case presents some features which are not typical for the syndrome (lipoma, pre-auricular appendages), we may most likely consider it as a representative of the disease.

The second case described by Everberg, Ratjen & Sørensen (1963 *a*) is more typical though unilateral. They examined their case, also a male, in greater detail as did Franceschetti & Klein. The patient presented Klippel-Feil's anomaly; he was incapable of external rotation of the eye balls. On lateral gaze the adducted eyes became retracted. On the right there was no hearing and irrigation of the right ear with icewater gave no vestibular response. On the left hearing as well as the vestibular function were normal. Polytomography of the temporal bones revealed the following results: at the left side there were found normal middle ear, ossicles, semicircular canals and cochlea. At the right side the external auditory meatus, middle ear and ossicles proved to be normal. The internal auditory meatus was short, the vestibulum was visualized as a small transverse oval translucency in the normal site, the cochlea was normal but semicircular canals were absent. The family history did not reveal any relevant abnormalities.

THE PRESENT INVESTIGATION[1]

Three females presenting the syndrome were examined otologically as well as radiologically. As we do not yet dispose of a polytome the following X-ray projections—as far as the limitation of neck movements permitted—were used: Stenvers projection and transorbital projection, tomography being used at one or both sides. Moreover a caloric examination of the peripheral vestibular organ was performed. With regard to the interpretation of roentgenograms of the os petrosum the following remarks are to be borne in mind. In general it is possible to ascertain the presence of cochlea, vestibulum, semicircular canals and meatus acusticus internus. Tomography is a useful complementary expedient to this ascertainment, especially if a polytome can be used. If one has only the possibility of linear tomography (as we had) it is not advisable to go too far with a precise diagnostical interpretation. Thus we did not dare to speak of hypoplasia in cases in which the contours of cochlea and canals became not very well visible, but we did indicate in the sketches what in our opinion appeared both well and less well. The results of our investigations were as follows.

1. A woman, now 2[illegible] years of age, former pupil of the Royal Institute for the Deaf at Groningen, the oldest of [illegible] children, and described as early as 1952 by Wildervanck. She shows the typical Klippel-Feil anomaly and

[1] We are much indebted to Dr C. Everberg, [illegible] Hospital, [illegible] the investigation.

the a-k-p tomographs of the petrosa, though not very distinct at the left and also insufficient at the right side, show cochlea and vestibular structures

If we summarize and compare the vestibular and radiological findings of our patients (see also pictures) and those of the patients radiologically examined by Franceschetti & Klein and by Everberg Ratjen & Sørensen, we can state that the loss of hearing seems to be attended by abnormalities of the os petrosum and the inner ear In our second case (picture upper row) where there is a remnant of hearing at the right side in the low frequencies until 3000 Hz, the bony labyrinth seems to be least underdeveloped At this side there was a good caloric reaction At the other side the vestibular function was absent as was the case at both sides in cases 1 and 3 In the case of Franceschetti & Klein the vestibular function was not examined, in the unilateral case of Everberg *et al* it was absent In both cases of the literature the bony labyrinth was underdeveloped

Though the number of patients examined is still small, we get the strong impression that the bony labyrinth is not normally formed in our cases These malformations are essential for hereditary labyrinthine progressive deafness but in this form of deafness the underdevelopment is much more severe In the common form of recessive deafness the bony labyrinth in the majority of cases is perfectly formed (not in *all* cases as mentioned erroneously in the table published by Grimaud *et al* *l c* [1])

In about one third of cases there has been found an abnormal or absent caloric response In unilateral deafness in most cases X-ray pictures revealed normal labyrinthic appearances Vestibular function was lacking at the deaf side only in 28% In the two patients showing Waardenburg's syndrome the bony labyrinth was normal and in one of them where the vestibular function was tested, caloric response was normal In the two brothers presenting the syndrome of deafness with split hand and split foot X ray pictures were completely normal The same is the case in patients with Pendred s syndrome Usher's syndrome and in cases of deafness associated with E C G abnormalities

Comparing the radiological and vestibular findings in the patients presenting the cervico oculo-acusticus syndrome with those in other forms of endogenous forms of deafness it seems to us that we are qualified to

[illegible] patients showing the syndrome should be recommended in order to check the radiological pictures of the bony labyrinth

ZUSAMMENFASSUNG

In drei weiblichen Taubstummen die das Zerviko-Okulo Akustikus Syndrom (Innenohrtaubheit mit Klippel Feil Anomalie und Abduzens Lähmung) aufwiesen

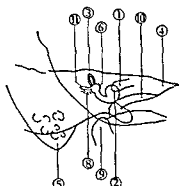


Fig. 2. Schematic representation of the normal petrous bone in Stenvers projection (partly after Mayer). *1* Meatus acusticus internus. *2* cochlea. *3* superior semicircular canal. *4* apex pyramidis. *5* mastoid. *6* vestibulum. *8* posterior semicircular canal. *9* mandibular condyle. *10* carotid canal. *11* lateral semicircular canal.

reaction. *X-ray examination* (see sketches middle row) (Fig. 1): at both sides the tomographic pictures of the ossa petrosa show incomplete cochlear and vestibular structures. For comparison a sketch of a normal os petrosum is added (Fig. 2).

2. A girl, pupil of the Institute for the Deaf, born as the third of 4 children in 1953, has been described already by Wildervanck (1960 *a*). She displays a torticollis to the left side, Klippel-Feil anomaly, an epibulbar dermoid on the left eye bulb (not typical for the syndrome). All eye muscles are well functioning. Three cousins in the third degree showed rachischisis, hydrocephalus and epilepsy respectively. An uncle in the eight degree suffered from epilepsy, too, and an aunt in the fifth degree had club feet. The parents are not related to each other. The examination revealed the following results. *Hearing*: at the right side only a remnant of hearing up to 3000 Hz with a loss of hearing in this region of about 90 dB. At the left side no reaction at all. Eardrums normal, manubrium mallei distinct. *Caloric examination*: at the right side normal reaction, at the left side reaction absent. *X-ray examination* (picture upper row) (Fig. 1): both the petrosa are well pneumatisized, at the right somewhat more than at the left. Bilaterally the internal meatus and the vestibular and cochlear system are visible. They seem however to be underdeveloped.

3. Also a female, born in 1951, last of 4 children, pupil of the Institute for the Deaf. She has been described shortly by Wildervanck (1960 *a*, patient D). She presents Klippel-Feil anomaly, abducens palsy of both eyes without demonstrable retractio bulbi. There is no consanguinity between the parents. A paternal cousin had a unilateral microtia and a deformed face and died at the age of 9 months. Our present investigation gave the following results. *Hearing*: at the right side a small remnant of hearing up to 1500 Hz with a loss of hearing of about 90 dB. At the left side fully deaf. Eardrums normal, manubrium mallei distinct. *Caloric examination*: left as well as right no reaction. *X-ray examination* (picture lower row) (Fig. 1):

ENDOLYMPHATIC HYDROPS REVEALED BY GLYCEROL TEST

Preliminary report

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From the Departments of Otolaryngology and Audiology (Heads Prof C A Hamberger and Ass Prof L Holmgren) and the Department of Neurology (Head Prof E Kugelberg), Karolinska Sjukhuset Stockholm

Single doses of glycerol 1 5 g/kg body weight orally, produced significant hearing threshold shifts in cases of Menière's disease with fluctuating hearing loss No effect was seen in more advanced Meniere cases with non fluctuating flat loss or in cases of perceptive deafness of less specific types The observations indicate that endolymphatic hyper tension is of direct importance for the fluctuating hearing loss in Meniere s disease A glycerol test may be adopted as a simple and rapid method for separation of reversible Meniere cases from irreversible cases of the disease and from other cases of perceptive deafness where endolymphatic hydrops is not involved

Endolymphatic hydrops has been demonstrated histologically in Meniere cases most recently in a paper by Schuknecht (1963) As pointed out, the importance of the hydrops for the symptoms is not clear These may alternatively be produced solely by the underlying disturbance which is still unknown and possibly of biochemical nature

The fluctuating low frequency loss of perceptive type which is characteristic of the early stages of Menière's disease gives the impression of being directly related to variable endolymphatic hydrops Consequently, dehydration therapy of various forms has been tried The effect has been difficult to interpret because of the extremely variable and irregular spontaneous course of the disease Recently, however, conclusive results have been obtained in a double blind study with long-term treatment with hydrochlorothiazide (Klockhoff & Lindblom in preparation) Statistical analysis revealed that this drug produced a partial relief of the symptoms at the fluctuating stage No improvement was observed in more advanced cases with a flat hearing loss of non fluctuant type It was assumed that hydrochlorothiazide reduced endolymphatic hydrops by interference with the water electrolyte balance

Against this background the effect of glycerol on hearing loss was studied in a series of cases of Menière's disease The presumption was that endolymphatic hydrops is of importance for the fluctuating hearing

zeigte die roentgenologische Untersuchung, dass das Labyrinth (Schnecke und Vestibularapparat) unvollständig entwickelt war. Nur bei einer Patientin war die vestibuläre Funktion an einer Seite erhalten. Diese Befunde bestätigen die *Auffassung, dass das Syndrom eine selbständige,* von den anderen Formen endogener Taubheit verschiedene nosologische Einheit ist. Die Verfasser geben eine Übersicht über die roentgenologischen und pathologisch-anatomischen Befunde bei anderen Formen endogener Taubheit.

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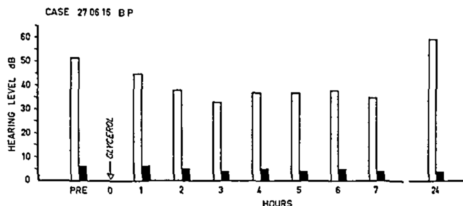


Fig 1 The low frequency hearing loss (mean at 250, 500 and 1000 Hz) before and after intake of glycerol 1 5 g/kg body weight in a unilateral case of Meniere's disease White and black staples refer to the pathologic and normal ear respectively

loss and might be influenced by the osmotic effect of glycerol It is known that glycerol causes a transient reduction in intraocular pressure (Virno *et al*, 1963).

MATERIAL AND METHODS

Ten cases of Meniere's disease with the typical symptom triad were selected In six of the cases the hearing loss was still of the fluctuating low frequency type The other 4 cases were of the more advanced type with mainly flat hearing losses In two of these the hearing loss had been static for a considerable time while in the other cases just noticeable fluctuations might still occur on rare occasions

The test was also performed on 3 control cases of unilateral perceptive deafness The origin was unknown but recruitment was complete indicating cochlear dysfunction

A standard dose of glycerol, 1 5 g/kg body weight, was given orally on empty stomach mixed with an equal volume of isotonic sodium chloride A few drops of lemon juice were added and the solution was served cold to reduce the slightly greasy and rather sweet taste Tone audiometry was performed immediately before the intake of glycerol and hourly during the rest of the day Another audiogram was taken on the following morning

As an index of the glycerol effect the average hearing loss at 250 500 and 1000 Hz was used These frequencies are representative for the low frequency loss of the disease Symptoms such as tinnitus, vertigo and "tightness" of the affected ear were also noted

RESULTS

In all 6 cases with fluctuating low frequency loss the glycerol intake was followed by a rapid hearing improvement The threshold shift was significant (>5 dB) after 1 hour, the maximum effect being obtained after

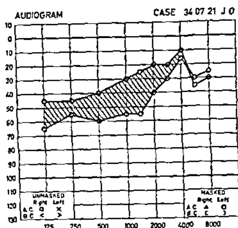


FIG 2 Hearing threshold shift induced by glycerol (orally 1.5 g/kg body weight) in a unilateral case of Menière's disease Shaded area indicates hearing improvement 2 hours after intake Hearing threshold of the normal ear not shown since it was not significantly influenced

2 or 3 hours The magnitude of the threshold shift was 10–23 dB with an average of 17 dB Those patients who had tinnitus and "tightness" noted a concomitant reduction of these symptoms All improvements were transient. On the following day, the hearing threshold had returned to the same level as before the glycerol intake In 2 cases the hearing loss was slightly more marked which was interpreted as a rebound phenomenon (Fig 1). The hearing thresholds of the normal ears were uninfluenced

The induced threshold shifts were limited to the low frequency range which is primarily concerned with the spontaneous fluctuations. A representative threshold shift is shown in Fig 2

Among the 4 advanced cases, no effect of the hearing threshold was observed in the 2 static ones whereas significant improvements, mainly in the consonant area and with considerable speech discrimination gain, occurred in the slightly fluctuating cases

In the three control cases of perceptive deafness no significant change of the hearing thresholds was obtained

As a side effect most patients noted a slight or moderate diffuse headache of 1 2 hours duration which appeared about half an hour after the glycerol intake A few patients experienced thirst

COMMENTS

Glycerol is easily absorbed and nontoxic in the dosage used (Johnson, Carlson & Johnson, 1933) Its effect is supposed to be a purely osmotic one The physical event underlying the glycerol effect in Meniere's disease may be a reduction of the endolymphatic hydrops or of the intralabyrinthine pressure The headache which accompanied the hearing threshold shift

is best explained by a diminution of the intracranial pressure. A concomitant lowering of the perilymphatic pressure may be expected which indirectly would reduce hypertension in the endolymphatic system. An effect via osmotic inhibition of the secretion of endolymph or a direct osmotic action on the sensory cells seems to be precluded primarily by the short latency of the threshold shift (less than 1 hour). Irrespective of the mechanism, however, the effect of glycerol on the typical fluctuating hearing loss in Menière's disease implies that this hearing loss is partly due to hydrodynamic factors which increase the intracochlear impedance. In clinical practice, a glycerol test may be useful in the differential diagnosis of reversible Menière cases from irreversible cases of the disease and from perceptive deafness of other kinds.

ZUSAMMENFASSUNG

Einzeldosen von Glyzerin 1.5 g/kg Körpergewicht peroral eingenommen zeigten signifikante Gehörschwellenbesserungen in Fälle von Meniers Krankheit mit einer fluktuierenden Innenohrschwerhörigkeit hauptsächlich in den tiefen Frequenzen. Kein Effekt wurde in mehr avancierten Fälle dieser Krankheit mit einer Gehörschwelle von statischem und einem mehr horizontalen Typus oder in Fälle einer Innenohrschwerhörigkeit von einem weniger spezifischen Typus beobachtet.

Die Observationen zeigen, dass eine endolymfatische Hypertension von einer unmittelbaren Bedeutung für den fluktuierenden Gehörverlust bei Meniers Krankheit ist. Infolgedessen kann eine Glyzerintest als eine einfache und geschwinde Methode gebraucht werden um reversible Fälle bei Meniers Krankheit von irreversiblen Fällen bei derselben Krankheit und von Fällen einer Innenohrschwerhörigkeit, wo ein endolymfatischer Hydrops von keiner Bedeutung ist, zu unterscheiden.

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RELATION BETWEEN STRENGTH OF STIMULUS AND DURATION OF LATENCY TIME IN VESTIBULAR ROTATORY NYSTAGMUS

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It is pointed out that no systematic study has previously been made of the relation between strength of stimulus and duration of latency time in vestibular rotatory stimulation with per rotatory recording of nystagmus Sixty healthy subjects were rotated at different strengths of stimulus in 3 series i e from 0.1 to 1°/sec², from 0.5 to 2°/sec² and from 2 to 8 sec² The latency time was determined from the start of stimulation to the first nystagmus beat A consistent relation is demonstrated between strength of stimulus and duration of latency time The absolute standard deviation of the latency time decreases with rising strength of stimulus but the relative standard deviation is largely the same in the whole material Although the results suggest an exponential relation between strength and duration no such relation can be demonstrated A critical point is obtained at an acceleration of 2° sec² It seems that below this value central factors can more easily influence the latency times than is the cases with stronger stimuli

Barany's rotatory test initiated an epoch during which it was considered that the function of the vestibular organ could be evaluated by recording postrotatory nystagmus However following the introduction of *cupulometry* by van Egmond Groen & Jongkees (1948) it was soon found that Barany's rotatory test was too strong and often gave rise to lengthy changes in the mode of reaction of the labyrinth Consequently the use of weaker stimuli has generally been adopted while continuing to base the evaluation on postrotatory reactions (Waletz 1933 Jongkees & Klijn 1956 van Egmond Groen & Jongkees 1948 Jung & Tonnies 1948 Aschan *et al* 1952 Mittermaier 1954 Jongkees 1956 van der Vis 1957 de Wit 1957)

Since the demands in evaluation of the vestibular organ's function have become increasingly stringent new methods of examination have been devised Instead of using brief relatively strong stimuli—as in postrotatory tests the organ is exposed to constant continuous and more lengthy stimulation with recording of the reactions during rotation Thus Montandon and co-workers (1954 1955) elaborated a method by which they made electronystagmographic measurements during the course of rotation By

exposing the patient to successively increasing acceleration from 0.4°/sec² to 2°/sec², they endeavoured to establish the threshold value of the nystagmus elicited. The threshold was defined as the acceleration required to elicit nystagmus during the whole duration of stimulation, but not at all after it. On the basis of a large series of recordings, they calculated that the threshold lay between 1/2° and 2°/sec².

Russbach (1955) utilized Montandon's technique and, using the same definition of the threshold, gave a mean value of 0.77°/sec².

Fumeaux (1958), claiming that Ewald's second law implies a preponderance of the ampullopetal effect over the ampullofugal, presumed that extremely slow acceleration would result in isolated stimulation of one of the lateral semicircular canals only. He made per-rotatory studies with the same technique as that used by Montandon *et al.* and by Russbach, and with the same definition of the threshold. He did, however, set up additional criteria, *i.e.*, that the per-rotatory nystagmus must appear with a latency time ranging from 6 to 15 sec after the start of stimulation, that nystagmus must last for practically the whole duration of acceleration, and that it must either cease less than 5 sec before the end of acceleration, or not continue for more than 5 sec after it. The mean value of the threshold according to his definition was 0.92°/sec². The latency time ranged from 2 to 41 sec, which gave a mean of 10 sec. In 90.9 per cent of the subjects tested, nystagmus started from 6 to 15 sec after the start of acceleration. Fumeaux concluded from his results that no correlation exists between strength of stimulus and latency time.

With successive improvements in the recording methods, increasingly weak nystagmus can be registered. Thus, Pfaltz & Richter (1956), Richter & Pfaltz (1956), Pfaltz (1960) and Decher (1962) demonstrated that nystagmus could be recorded already with an acceleration of 0.1 to 0.4°/sec². Ek, Jongkees & Klijn (1959) stated that measurements of the threshold value are, actually, a measure of the sensitivity of the method rather than a true expression of the stimulation threshold of the sensory organ.

A study of the threshold value for nystagmus implies trying to activate a reflex arc so that it reacts according to the definitions set up for this threshold. This seems, in the individual case, often to have been a task requiring several examinations before any accurate value could be given. Consequently, a number of authors have observed the latency times instead and found, at first glance, that these were longer with weak stimuli than with stronger ones (Mulder, 1908; Mittermaier & Rossberg, 1956; Decher, 1962; Tsuiki *et al.*, 1963). Mulder (1908) stated that the intensity of the reaction was in some relation both to the strength of acceleration and to its duration. His statement was based on the assumption that the product of these two factors is constant. Jongkees (1953) was, however, able to demonstrate that "Mulder's law" is valid only within certain ranges of acceleration.

It is thus evident from the literature that the data on the relation be-

tween the strength of stimulation and the latency time for the appearance of nystagmus are exceedingly few and sometimes even conflicting As far as we have been able to ascertain no systematic study has ever been made to establish the dependence of the latency time on the strength of stimulation The present study was made for this purpose

CASE MATERIAL AND METHODS

Case material

Sixty subjects were used for the investigation chiefly women aged 20-40 years About 1/4 were physiotherapy students 1/4 were nurses and ward maids and the remainder consisted of patients with diseases that were considered unable to affect the results Only persons in good general condition with normal hearing and without disturbances of balance, systemic diseases or fever were included It was also ensured that none of the subjects had been given any medication that might influence the results

Apparatus for stimulation

For the investigation we used a rotation chair (Stille Werner modification Fluur) in which the subject sat with his head secured in a holder and inclined 30° forward It was checked that the chair s axis of rotation was directed on a point halfway between the subject s ears A special stand fixed to the ceiling was used for this purpose

The chair could be accelerated and decelerated with known stimuli adjustable on a dial in °/sec² from 0 1 to 10°/sec² and the speed kept constant for a given time The speed of the chair could be read off constantly on a galvanometer

Mode of stimulation

The ideal procedure for a study of the relations between acceleration and latency time would be for each subject to be stimulated a large number of times with acceleration of varying strength between e g 0 5°/sec² and 8°/sec² to provide a series of latency times In a preliminary study in about 20 subjects it was however found that such investigations took a great deal of time and that many of the subjects became markedly listless towards the end of the investigation This was considered to affect the results The large number of stimulations might also be envisaged to induce habituation and fatigue and such factors must obviously be avoided

We therefore confined ourselves to using 4 different strengths of stimulation at each examination The experiments were divided into the following series

Series 1 0 1° sec² 0 3°/sec² 0 5°/sec² and 1°/sec²
Series 2 0 5°/sec² 1°/sec² 1 5°/sec² and 2°/sec²
Series 3 2°/sec² 4° sec² 6°/sec² and 8°/sec²

The experiment was preceded by a preliminary test. The chair was accelerated with a strength of stimulus within the intended measuring series, i.e., as a rule 0.5°/sec² in series 1, 1°/sec² in series 2 and 2°/sec² in series 3. At a speed of 20 to 40°/sec, a change was made to a constant speed for 2 min. The chair was then decelerated at the same intensity as before. This preliminary test served to check the subjects' reactions, the function of the chair and the recording apparatus. In addition, it familiarized the subjects with the course of events, so that they could sit calmly and relaxed from the start of the experiment.

After a few minutes' rest, the actual experiment was started. In series 1, the chair was first accelerated at 0.1°/sec² to 15 × 0.1°/sec² = 1.5°/sec, and after at least 2 min at constant speed was decelerated to stationary. If no nystagmus resulted, the same acceleration was continued to 30 × 0.1°/sec² = 3°/sec, a constant speed for at least 2 min, and then deceleration for 30 sec at 0.1°/sec². In series 1, the times used were 15, 30 and 45 sec. When nystagmus had been distinctly observed in a deceleration, the next highest stimulus was applied. If distinct nystagmus had been elicited with stimulation at 0.1°/sec² for e.g. 30 sec, the next higher stimulus was applied for 15 sec, giving an initial speed of 15 × 0.3°/sec² = 4.5°/sec. If no nystagmus was elicited, speeds of 30 × 0.3°/sec² and 45 × 0.3°/sec² were tested. If nystagmus was then elicited or if—despite the 45 sec long stimulation—no nystagmus was recorded, the next intensity was applied, i.e., 0.5°/sec², the initial speed being calculated to be 15 × 0.5°/sec² = 7.5°/sec, and so on.

In series 2, shorter durations of stimulation were required to elicit nystagmus. We used 5, 10, 20 and 30 sec, the procedure being on the same principles as in series 1. Series 3 was performed in a similar way, the times being 2, 4, 6 and 8 sec.

Grouping of the material

We investigated groups of 20 subjects, who were tested according to each series. Generally, each subject was tested on only one occasion, but in some cases a subject was tested in different series, at an interval of at least several days. As a rule, the acceleration series was decided before starting the experiment and, even if no lots were drawn, we aimed at a completely random distribution. Moreover, the matter of main interest was, in fact, the reactions of the individual subject.

Recording

The recording was made with silver electrodes placed at the outer canthus of each eye as close as possible to the eyeball. The subject's eyes were open behind a diving mask which excluded incoming light. The impulses were transmitted to a nystagmograph (Schwartzer), with 8 channels set at different degrees of amplification. These were arranged so that the channel with the highest amplification gave an amplitude of 12 mm for 50 microvolts, whereas the amplitude for the lower amplifications in

order was approximately 10, 8, 4 and 2 mm The object of this setting was to be able to include extremely weak nystagmus, and for it to be distinctly recorded on the channels with the highest amplification, and at the same time to record even extremely strong eye movements in their entirety on the channels with weaker amplification To further facilitate distinction between a blinking movement and nystagmus, two channels were rectified in different directions Thus, one recorded only eye movements in one direction, and the other movements in the opposite direction This implied that blinking produced simultaneous discharges on both channels, whereas a nystagmus beat was recorded on one channel only

The speed of the paper was 1 5 cm/sec The time constant was 0 1 sec on all channels, and automatic second marking was always connected

Before each stimulation, the subject was instructed to sit relaxed, to avoid unnecessary blinking and to direct his gaze calmly forwards without fixating the eyes The eye movements were then recorded for about 10 sec before starting deceleration, and then during deceleration until the chair was stationary The latency time was regarded to be ended when the first definite nystagmus beat was recorded In group 3, the measurements were made to within 1/4 sec, and in the other groups to within 1 sec In cases with disturbing blinking or voluntary eye movements during the course of stimulation, the test was repeated after a few minutes' pause This was, however, necessary on only two occasions

RESULTS

Most of the subjects in series 1, in which the strength of the stimuli was weakest reacted in a way that was exceedingly hard to determine In the cases in which acceleration of 0 1 or 0 3°/sec² did elicit any observable nystagmus it was initially so weak and differed so little from the artefacts commonly associated with electronystagmography, that no accurate measurements of the latency could be made A few subjects in this group reacted with distinct nystagmus during stimulation with 0 3°/sec² However in most cases this intensity elicited only occasional nystagmus beats or sometimes sequences of them, but in every case the first beats were so weak that no definite determination of the latency time could be made here either Although more than 20 examinations were made, the number of curves that could be evaluated were so few that, in our opinion, stimuli weaker than 0 5°/sec² failed to give any accurate results

Series 2 with acceleration ranging from 0 5 to 2°/sec² was, on the other hand much easier to evaluate Good recording was achieved, and it was possible in a highly satisfactory way to determine exactly where nystagmus started The primary results are given in Table 1 It is seen that the latency time for 0 5°/sec² in the whole group ranged from 4 to 30 sec A study of the individual latency times at the following strengths of stimuli showed in most cases, a successive shortening At 2°/sec², the value was

TABLE 1. *Latency times for stimulation in the range 0 5–2°/sec²*

	Strength of stimulus (°/sec²)			
	0 5	1 0	1 5	2
Latency time (sec)	m > 30	8	5 5	3
	4	4	2 5	2
	13	14	2 5	2
	18	6	6	3
	15	8	4	4
	10	2	4 5	6 5
	15	6	4 5	3
	15	11	5 5	6
	7	9	3 5	3 5
	12	8	4	5
	10	10	8	5
	5	4	2 5	2
	6	7	2	4 5
	6 5	4 5	2	2
	4 5	3	3	4
	26	4	6	2
	13 5	1 5	4	2
	18	9	7	5
	8	3	3	2 5
	9	5	2 5	2 5
Sum of latency times	215 5	130 0	82 5	69 5
Arithmetic mean of latency times ($\bar{X}$)	11 3	6 5	4 1	3 5
Standard deviation ($\hat{S}$)	5 69	3 25	1 73	1 37
Coefficient of variation $\hat{S}/\bar{X} = C$	0 50	0 50	0 42	0 39
Arithmetic mean of log latency time	1 00	0 76	0 58	0 50

from 2 to 6 sec (mean 3 5 sec) In some subjects, the latency time was only slightly shorter at 2°/sec² than at 0 5°/sec², whereas in others there was an appreciable shortening, to 1/10 or less In some series, we observed that the latency time could be prolonged when the strength of stimulus was increased, but this applied in only 6 cases

In group 3, the latency times in the stimulation range up to 8°/sec² were much shorter In the first test, i e , 2°/sec², the time ranged from 1 to 6 5 sec, no nystagmus was, however, elicited in 4 cases, despite stimulation for 8 sec, which was the maximum in this group The next intensities of stimulation gave increasingly shorter latency times Thus, at 4°/sec² the mean was 3 0 sec, this was further reduced to 2 3 and 1 7 sec at 6° and 8°/sec², respectively The individual course—in which an increase in latency time was occasionally observed with rising intensity—can be followed in Table 2 As in group 2, some subjects had approximately the same latency time despite rising intensity of stimulus, whereas others showed a marked shortening under the same conditions

A survey of the results is plotted in Fig 1, in which the intensity

TABLE 2 *Latency times for stimulation in the range 2–8°/sec²*

	Strength of stimulus (°/sec²)			
	2	4	6	8
Latency time (sec)	5	2	1	1
	5 5	2	2	2
	6 5	2	2	1
	5 5	2	3	2
	6 5	4	1	2
	m > 8	6	2	1
	m > 8	5	5	3
	1	2 5	1	1
	3	3	1 5	2
	3 5	1 5	0 5	1
	6	2	3	2
	6	5	4	2
	m > 8	3	2	0 5
	4	4	3 5	2
	2 5	2 5	2 5	4
	5	4	3	1
	2	2	2	2
	m > 8	4	3 5	3
	1	1	2	1
	1 5	1 5	1 5	1
Sum of latency times	61 5	59 0	46 0	34 5
Arithmetic mean of latency times ($\bar{Y}$)	4 0	3 0	2 3	1 7
Standard deviation (S)	1 98	1 19	1 22	0 88
Coefficient of variation $S/\bar{X} = C$	0 50	0 40	0 53	0 52
Arithmetic mean of log latency time	0 53	0 42	0 30	0 18

of stimulus is given in °/sec² on the ordinate and the latency time in sec on the abscissa Series 2 is plotted below the line a–b and series 3 above it

It is seen in the lower parts of the diagram that at the lower intensities of acceleration the latency times are relatively long as well as scattered over a large time range This is already less with the use of 1°/sec², and at 2 to 4°/sec² still less scattering is observed and also a slight displacement of the accumulations of dots to the left This applies as well to still higher situated accumulations of dots representing 6 and 8°/sec²

In order to ascertain whether the results followed an exponential curve Fig 2 was plotted Line *a b* has the same meaning as in Fig 1 As in Fig 1 the acceleration is given on the ordinate whereas the latency times have been converted to logarithms and are plotted on the abscissa It is seen that the log latency times for the stimuli exceeding 2°/sec² have an almost linear exceedingly steep course The curve then deviates suddenly at an acceleration of 1 5 to 2°/sec², and below this value changes direction, its course being partly straightened

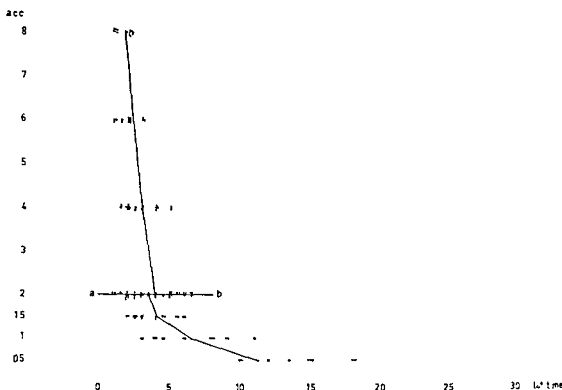


Fig. 1. Relation between strength of stimulus and duration of latency time.

DISCUSSION

In an investigation of this kind, it must be borne in mind that one is not measuring the sensitivity of the peripheral vestibular organ. What one does, in fact, determine is the stimulability of the whole reflex arc passing from the vestibular apparatus to the ocular muscles. This is because the following events occur during the latency time: (*a*) the endolymph is set in motion and the cupula starts to deviate, (*b*) the flow of electrical impulses in the vestibular nerve is altered, (*c*) transmission of impulses in the synapses starts, (*d*) the ocular muscles are activated, and the eye deviates slowly to one side. The latency time is ended with the appearance of the first nystagmus beat. Thus, this takes place much later than the peripheral organ's rapidly starting flow of endolymph in response to stimulation (Schmaltz, 1925), and the accompanying increase in the flow of impulses in the vestibular nerve (van Eyck, 1955, Trincker, 1962).

If one wishes, in the strict sense, to measure the latency time of the reflex arc, the time should be recorded from the onset of stimulation to the instant when the eyes start their slow deviation. However, since this is exceedingly difficult to do in man, it has been decided to measure the reaction after the rapid phase, which is easier to observe. It is evident from the curve in Fig. 1 that long latency times are obtained with weak stimulation, whereas the time decreases successively with stronger stimuli.

The question arises whether lengthy stimulation with such weak ac-

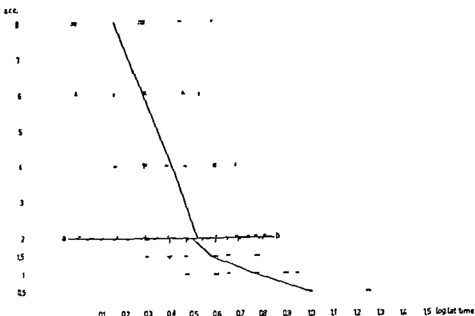


Fig 2 Logarithmic relation between strength of stimulus and duration of latency time

celeration as that used in series 1 can, finally, elicit nystagmus owing to a 'Bahnung" in the reflex paths This is regarded as improbable (Decher, 1964 Montandon & Dittrich, in prep) Nor is it likely that a stimulus which, after 90 sec, has failed to elicit any nystagmus would, by longer duration, be able to produce nystagmus as a result of some central mechanism It is our experience that a stimulus which, after about 45 sec, has not elicited any definite nystagmus, will not do so even if its duration is considerably prolonged

Table 1 and Fig 1 also show that there is a great scattering in the latency times between different subjects at the low intensities of stimulation but that it decreases with rising strength of acceleration The coefficient of variation is, however, largely the same in all groups, although it decreases in the range 1 5 to 4°/sec² That a higher coefficient of variation is obtained at low accelerations may depend on biological factors whereas the increase recorded with stronger stimuli is probably to be ascribed partly to measuring errors In these ranges the measurements are made only to within ¹/₂ sec Lower values would certainly have been obtained if it had been possible to measure in tenths of a second

Even if the absolute scattering is directly proportional to the strength of stimulation the coefficients of variation show that the relative scattering is the same for all stimuli tested, except 1 5, 2 and 4°/sec², where it is slightly less

At an acceleration of 2°/sec², it is found that the latency times differ

somewhat if the subject starts the test with this strength of acceleration or ends the experimental series with it This can presumably be explained by the excitatory state in the reflex pathways being greater when the subject has undergone the same test shortly before than when the strength of acceleration in question initiates the experimental series

Interesting features are found among the individual results Thus, the subjects in group 1 (Table 1) who, at an acceleration of 0 5°/sec², had a fairly long latency time (15 sec and more) in relation to the other subjects in this group, were found at the next intensity of stimulus (1°/sec²) to have a latency time largely in agreement with that of the group as a whole *Consequently, this must not be interpreted to imply that these subjects* had a poorer ability to react than the others in this group In their case, the reflex was not so easily elicited in the first test, but the excitability was *already* greater *in the next test* Psychological factors *presumably play* a considerable role in this respect In general, a continuous decrease in the latency time was noted at higher intensities of stimulation However, a few cases in each group showed an inappreciable increase compared to the previous stimulation These varying patterns of reaction may have depended on differences either in the sensitivity of the peripheral sensory organ, or at one or more sites in the path of the impulses to the effector organ We do not know the exact reason for these different reaction patterns

Fumeaux (1958), in his studies of the vestibular threshold, focused attention on latency measurements only in the acceleration range 0 8 to 1 2°/sec². He showed that in 90 9 per cent of his material, the latency time was from 6 to 15 sec, at his threshold value of 0 92°/sec² This gives a mean value of 8 5 sec Although we have not made any analysis of the reactions around the aforementioned threshold value, a study of the latency time at an acceleration of 1°/sec² shows a variation from 2 to 14 sec In 90 per cent of this material, the latency time ranged from 2 to 10 sec The mean value in this group was 6 5 sec Cautious interpolation with the help of Fig 1 shows that the mean of our values at 0 92°/sec² would be about 7 sec, i e, somewhat lower than Fumeaux's figure No *definite* conclusion can, however, be drawn, since our material was so much smaller than his

Mittermaier & Rossberg (1956) also showed that the latency time for *per-rotatorily elicited nystagmus in the range* 1 to 4 5°/sec² is somewhat longer with weaker intensities of stimulus There are, however, no possibilities of comparing these investigations with ours, as Mittermaier's results were *given only in the form* of *curves, and no data* are available on the size and composition of the material, nor on the primary results

A superficial study of the strength-duration curve (Fig 1) gives the impression *that it has an* exponential course To *ascertain* whether this was actually so, the results were converted to logarithms A straight line could have been expected, but this was not the case (Fig 2) Instead, a

fairly sharp notch was present between two otherwise relatively straight lines at a point corresponding to an acceleration of 2°/sec². This must be interpreted in one of two ways, i.e. the curve is not, in fact, exponential or a change in the biological event takes place precisely at 1.5 to 2°/sec². There seems to be a critical point here, which cannot be explained by the results. The frequency of impulses from the sensory organ seems to have reached such an order of magnitude that the central reflex time is shortened. This implies that central factors appear to play a considerably greater role in stimulation below 2°/sec² than when stimulation is above this level.

ZUSAMMENFASSUNG

Eine systematische Untersuchung über die Beziehung zwischen Stärke und Dauer bei vestibulärer rotatorischer Stimulation und perrotatorischer Registrierung von Nystagmus ist bisher noch nicht unternommen worden. 60 normale Personen wurden mit verschiedenen Beschleunigungsstärken in 3 Serien von 0.1-1°/Sek.² 0.5-2°/Sek.² und 2-8°/Sek.² rotiert. Die Latenzzeit vom Anfang der Stimulation bis zum ersten Nystagmusschlag wurde bestimmt. Ein gesetzmässiges Verhältnis zwischen Stärke und Dauer wurde festgestellt. Die absolute Verbreitung der Latenzzeit nahm mit zunehmender Stimulationsstärke ab, aber die relative Verbreitung war im grossen ganzen dieselbe im ganzen Material. Die Resultate deuteten auf eine exponentielle Beziehung zwischen Stärke und Dauer, aber dies konnte nicht nachgewiesen werden. Einen kritischen Punkt erhielt man bei einer Beschleunigung von 2°/Sek.². Bei niedriger Stärke scheinen zentrale Faktoren eine grössere Rolle als bei stärkeren Stimuli zu spielen.

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ISOLATION OF RESPIRATORY SYNCYTIAL VIRUS FROM MIDDLE EAR EXUDATES OF INFANTS

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Specimens from the middle ear exudate were obtained from children during a respiratory syncytial virus epidemic in Turku Finland in 1965 By puncture aspiration through the ear drum and immediate direct inoculation of the exudate specimens obtained into cell cultures respiratory syncytial virus was isolated from one or both ears of 9 infants 12 months or younger hospitalized for a disease of the lower respiratory tract caused by the respiratory syncytial virus

INTRODUCTION

Reilly *et al* (1961) have reported catarrhal otitis media in 17% of children infected with respiratory syncytial (RS) virus and Kapikian *et al* (1961) observed redness of the tympanic membranes in about 50% of children with pneumonia and an associated RS virus isolation

During an outbreak of respiratory illness caused by RS virus in Finland at the end of 1963 and the beginning of 1964 the frequency of otitis media in children with RS virus infection was 25% (Berglund, Vihma & Wickstrom 1965) Although in most instances the middle ear infections appeared to be caused by bacteria as evidenced by the severity of the symptoms the possibility of a concomitant or preceding infection of the middle ear by RS virus could not be excluded

Consequently as the following RS virus epidemic started in Turku in 1965 attempts were made to isolate RS virus from the ears These attempts were successful (Berglund & Ståhlmann 1966), and RS virus was isolated from the middle ear exudates of 2 children with otitis media This led us to undertake a more systematic study with an improved technique, on the occurrence of RS virus in the middle ear

This report describes the isolation of RS virus from the middle ear exudates of several infants with middle ear infection accompanying a lower respiratory tract illness caused by RS virus

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MATERIAL

The study was carried out in the course of an RS virus epidemic which extended from the beginning of April to the end of June, 1965 All the children were studied during a 16-day period in June just before the epidemic ended The material consists of all those children who visited the Out-patient Department of the Otolaryngological Clinic for acute symptoms and signs of middle ear infection, and all the children in the wards of the Pediatric Clinic, University of Turku, with an acute respiratory tract illness and signs of middle ear affection A total of 27 subjects was studied Twelve children were seen at the out-patient clinic Their ages varied from 4 months to 4 years, the mean age being 20 months Fifteen children were treated on the wards Their ages varied from 2 months to 3 years, the mean age being 9 months

METHODS

A continuous cell line of human amnion cells strain Utrecht (U cells) obtained from Dr R Doorschodt, Hygienisch Laboratorum der Rijks Universiteit, Utrecht, Holland, was used for all virus isolations The cells were grown in tubes in Hank's balanced salt solution with 0 5% lactalbumin hydrolysate and 25% inactivated calf serum The maintenance medium of the cells consisted of minimum essential medium supplemented with 5% tryptose phosphate and 5% inactivated horse serum and containing 800 units of penicillin, 800 micrograms of streptomycin, 25 units of nystatin and 5 micrograms of amphotericin B per ml

After the addition of 2 ml of fresh maintenance medium to each tube, inoculation of the tubes was carried out within 3 days The tubes were incubated in stationary racks at 35°C before and after inoculation The cultures were examined every day or every other day and refed with fresh maintenance medium twice a week In a few instances of non-specific degeneration of the cells a second passage was carried out before the final examination If the cultures did not show cytopathic effects 2 weeks after the inoculation they were discarded Cell cultures showing a definite cytopathic effect were frozen at −70°C in 50% glycerol, and subsequent passages were carried out 2–3 months later

The middle ear exudate specimens were obtained with a syringe and a needle by a puncture aspiration technique described by Lahikainen (1953) Before the puncture the external acoustic meatus was mechanically cleaned with a cotton stick dipped in alcohol No anesthesia was used for children under one year old, whereas those over one year of age were given general divinyl ether anesthesia After puncture of the middle ear one drop of the exudate withdrawn was immediately injected directly into a cell culture tube The syringes containing the exudate were then transferred to the Department of Medical Microbiology where bacteria were cultured and identified according to the methods described by Gronroos *et al* (1964)

After specimens had been taken from the middle ear exudates cell culture tubes were inoculated in duplicate with throat swab specimens a separate cotton applicator being used for each tube The fluid remaining in the cotton was pressed out by rubbing the swab along the inner surface of the tubes One throat swab specimen was obtained for bacterial examinations

Paired serum specimens were obtained within an interval of 2 to 5 weeks from most of the children treated on the wards whereas no serum specimens were obtained from those who visited the out patient clinic

A slightly modified microcomplement fixation (CF) method of Sever (1962) was used for the antibody titrations The sera were inactivated at 56°C for 30 minutes after which serial 2 fold serum dilutions of 0 1 ml volumes were made in tubes with veronal buffered saline beginning from a serum dilution of 1/4 CF antigen was prepared in U cells grown and maintained as described above Three antigens were employed in the CF test The Randall strain of RS virus as well as a virus isolate producing syncytial cell degeneration obtained from the middle ear exudate of one of the children included in the study and a cell control antigen The virus infected cultures and the control cell culture were harvested at the same time when the cell degeneration of the virus infected cultures was complete The cultures were frozen at −70°C and thawed 10 times before CF titration against 8 antibody units of a pool consisting of early convalescent phase RS virus immune sera obtained from 4 children Four antigen units and 2 full units of complement were employed in the test The reagents were distributed on the Plexiglas plates with syringes and cross cut hypodermic needles which were adjusted to deliver 0 02 ml of water/drop The unit volume used in the CF test was 1 drop The titer was the highest initial dilution of serum giving no more than a 1+ hemolysis as determined by visual estimation A control complement titration and a serum control as well as a titration of a serum with known Randall strain RS virus CF antibody titer were included in the test

Neutralization tests for the identification of RS virus isolates were carried out in U cell cultures grown and maintained as described above The RS virus immune serum used for identification was prepared in guinea pigs against the Randall strain which had been grown in BS C-1 cells maintained in 5% guinea pig serum All dilutions were made with Hank s balanced salt solution The virus suspensions which were unfrozen were spun for 15 minutes at 2000 r p m before use The immune serum was inactivated at 56°C for 30 minutes Equal parts of 1/10 dilution of virus and 1 10 dilution of immune serum were mixed and incubated at room temperature for 1 hour after which cell culture tubes containing 1 ml of maintenance medium were inoculated with 0 2 ml of the mixture Simultaneous virus titrations were performed by inoculating cell cultures with 10 fold dilutions of virus 0 1 ml/tube and 5 tubes/dilution Immune serum controls as well as control inoculations of cell cultures with mixtures

TABLE 1. *Clinical and laboratory data on 10 children in whom respiratory syncytial virus was isolated from throat swabs.*

Case No	Age in months	Duration in days of the respiratory symptoms before the first middle ear puncture	Time in weeks within which the middle ear signs disappeared after the first middle ear puncture	Volume of middle ear exudate obtained by the first puncture[a] Left ear	Right ear	Sedimentation rate[b]	Total leucocyte count[b]	Per cent age lymphocytes[b]	Clinical diagnosis[c]
1	3	14	1	+	+	22	5,500	65	Bronchopneumonia l dx
[illegible]	10	5	2	+ +	+ +	12	11,200	66	Bronchitis ac
[illegible]	7	5	1	+		15	10,800	45	Bronchopneumonia l dx
[illegible]	12	14	2	+ + +	+ + +	17	8,800	64	Bronchopneumonia l dx
[illegible]	5	5	2	+	+	6	7,900	48	Bronchitis ac
[illegible]	3	5	2	+		23	7,200	69	Bronchopneumonia l a
[illegible]	2	6	1	+ +	+ +	5	11,300	77	Bronchopneumonia l dx
[illegible]	8	8	1	+	+		15,900	64	Bronchitis ac
[illegible]	3	4	2		+ +	35	9,100	51	Bronchopneumonia l a.
[illegible]	21	3		+	+ +				Inf ac resp

[a] + indicates an exudate volume of <0 1 ml, + + 0 1–0 2 ml + + + 0 3 ml or more The volumes were estimated visually

[b] Determined from a blood specimen obtained within 2 days after the first middle ear puncture

[c] In some cases bronchiolitis could have been added to the diagnosis

of virus and normal guinea pig serum were included in the tests The cultures were incubated at 35°C and finally examined for syncytial cytopathic effects on the 5th day following inoculation Infectivity titers were calculated according to the method of Reed & Muench (1938) and expressed as the number of tissue culture infectious doses (TCD$_{50}$) per 0 1 ml of undiluted virus suspension

RESULTS

Children with virologically confirmed RS virus infection

This group consists of 10 children, all of whom had a positive RS virus isolation from their throat swab specimens and who were hence considered to be suffering from RS virus infection Nine of the children were 12 months or younger and treated on the wards They had been hospitalized for a severe acute illness of the lower respiratory tract One of the children was 21 months old, and visited the out-patient department for an upper respiratory tract infection (case No 10) Clinical and other data on the children are given in Table 1

TABLE 2 *Time of appearance and degree of the syncytial cytopathic effect in cell cultures inoculated with throat swabs and middle ear exudates of 10 children with respiratory syncytial virus infection* *

Case No	Age in months	Duration in days of the respiratory symptoms before puncture	Throat		Left ear	Right ear
			Tube 1	Tube 2		
1	3	14	+ + +		+	(+)
2	10	5	+ + +		+ + +	+ + +
		11			–	–
3	7	5	+ +	+ +	+ + +	
		12		(+)		–
4	12	14	+ +	+	+ +	+ +
5	5	5	+ + +	+ + +	+ + +	+ +
		11	(+)	–		–
6	3	5	+	+	(+)	
7	2	6	(+)	(+)	(+)	–
		9		–	–	–
8	8	8	+ +	+ +	+	–
9	3	4	+ + +	+ +		(+)
		6	–	(+)	–	–
10	21	3	+ + +	+ + +	–	–

* + + + indicates a syncytial cytopathic effect in 75 per cent + + in 50 per cent and + in 25 per cent of the cell sheet on the 4th to 6th day following inoculation (+) indicates a syncytial cytopathic effect appearing after the 6th day after the inoculation

At the otological examination one of the children (case No 2) was reported by her mother to have had a discharge from her left ear 4 days earlier and another (case No 8) was known to have rubbed her ears during the past days Only these two children could be demonstrated possibly to have had subjective symptoms from the ears

On examination, the ear drums were intact in all cases and did not show any typical signs of infection such as redness or injection There was also no typical roundness around the manubrium of the malleus or ballooning of the posterior part of the ear drums The ear drums appeared to be thin or at most slightly thickened The position of the ear-drums was normal and generally the reflex was still visible As a matter of fact the only sign of middle ear affection was a decreased mobility of the ear-drums as established by the use of Siegle's pneumatic speculum This sign was common to all of the children

The exudate obtained by aspiration puncture of the middle ear was serous or mucous and clear Seven children were punctured bilaterally and 3 unilaterally Of the 7 children punctured bilaterally 4 yielded an isolate of syncytial virus from both ears and 2 from one ear From the ears of one child (case No 10) no virus was isolated All 3 who were

TABLE 3. *Reciprocal respiratory syncytial virus complement fixing antibody titers of children with respiratory syncytial virus isolation from throat swabs. The sera were titrated against the Randall strain of respiratory syncytial virus and against a virus strain isolated from the ear*

Case No.	Age in months	Time in days after the beginning of the respiratory symptoms	Time in days after the puncture	Randall strain	Strain isolated from the ear[a]
1	3	16	2	<4	<4
		26	12	4	4
		49	35	<4	<4
2	10	11	6	32	32
		25	20	32	32
3	7	5	0	<4	<4
		39	34	<4	<4
4	12				
5	5	9	4	<4	<4
		53	48	16	16
6	3	5	0	<4	<4
		6	1	<4	<4
		13	8	<4	<4
		34	29	4	8
7	2				
8	8	14	6	32	32
		50	42	16	16
9	3	9	5	<4	<4
		19	15	8	4
10	21				

[a] *This virus strain was obtained in case No. 5 from the right ear exudate.*

punctured unilaterally yielded an isolate of syncytial virus from the ear. A second puncture was carried out on 5 children 2–7 days after the first puncture, but at the time of the second puncture virus could no longer be found in the middle ear exudates although the throat swab specimens still contained virus in a few cases. More detailed information on the time of appearance and degree of the syncytial cytopathic effect in the cell cultures is given in Table 2.

All the virus isolates obtained from the middle ear exudates and from the throat swabs were identified as RS virus. The anti-Randall strain immune serum used in the neutralization tests in a dilution of 1/10 always completely neutralized about 100 TCD_{50} units or less of the virus isolated. However, if more than 100 TCD_{50} units of virus were employed in the tests, the virus was neutralized to some extent by the immune serum but not completely although in the same test more than 3200 TCD_{50} units of the Randall strain of RS virus was completely neutralized by the same immune serum in the same dilution.

On culture the middle ear exudates obtained at the first puncture were found to be negative for bacteria in 4 cases *Staphylococcus albus* was isolated in 6 cases This bacterium usually considered non pathogenic for the middle ear was probably derived from the external acoustic meatus by the puncture Nine of the 10 children were receiving antibiotics at the time of the puncture At the second puncture the exudates of 3 children were negative for bacteria *Staphylococcus albus* was isolated in one case, and *Staphylococcus aureus* in one (Case No 9)

On culture all throat swab specimens were found to be negative for pathogenic bacteria

All signs of middle ear affection disappeared within one or two weeks after the first puncture as ascertained by examination carried out every 4 5 days

Paired sera of 7 children were examined for the presence of CF antibodies for the Randall strain of RS virus and for a virus isolated from a middle ear exudate The titers are shown in Table 3

It appears that the titers were of the same level with both the antigens and that 3 children out of 7 showed a 4 fold or greater rise in titer The titer of 2 children rose from < 1/4 to 1/4 One child showed a fall in titer from 1/32 to 1/16 and one child an equally high titer of 1/32 in the two serum specimens With a cell culture control antigen hemolysis was complete at the initial serum dilution of 1/4 of each serum specimen

The sera were also tested for CF antibodies to influenza viruses A B and C parainfluenza viruses 1, 2 and 3 mumps reo and cytomegalovirus, ornithosis and Eaton agent Fourfold or greater rises in adenovirus antibody titer were detected in case No 2 (from < 1/4 to 1/16), case No 3 (from < 1/4 to 1/32) and case No 8 (from 1/32 to ≥ 1/128) An increase of the cytomegalovirus antibody titer (from ~ 1/4 to < 1/4 to 1/16) was noted in one child (case No 1)

Case reports

Case No 2 This girl was 10 months old On April 25 1965 she visited the Out patient Department of the Otolaryngological Clinic for cough and rhinitis of one week s duration The ear status was normal Two weeks later on May 8 when she again visited the out-patient department She had a bilateral middle ear infection The ears were punctured and antibiotic treatment was initiated On May 29 she fell ill again with cough and rhinitis and on the next day she had a discharge from her left ear, according to her mother She was hospitalized for the respiratory symptoms on June 2 The diagnosis was acute bronchitis At the otological examination the following day the mucous membranes of the nose were found to be *swollen* and covered with clear mucous exudate the pharynx normal The ear-drums were thickened and dull but not reddish The position of the ear-drums was *normal* their mobility decreased 0 1–0.2 ml of mucous middle ear exudate was obtained by puncture from each ear RS virus was isolated from the exudate of both ears and from the throat swab *Staphylococcus albus* was cultured from the right ear The throat swab was *negative for* patho-

genic bacteria. At the time of puncture the patient was receiving antibiotics The titer of the first blood specimen, obtained 6 days after the puncture or 12 days after the beginning of the respiratory illness, was 1/32. The titer of the second blood specimen, obtained 2 weeks later, was also 1/32. Further data are given in Tables 1 and 2.

In this case RS virus was isolated from the middle ear exudate of both ears 5 days after the onset of a respiratory tract illness caused by RS virus Since the middle ear infection which was associated with the RS virus infection was complicated by discharge from the ear, the possibility cannot be definitely excluded that RS virus was involved in the process which resulted in perforation of the ear drum.

Case No 3.—This 7-month-old boy was hospitalized on June 3, 1965, for cough and fever. The clinical and x-ray diagnosis was bronchopneumonia Ia. *Streptococcus pyogenes* was isolated from the throat swab taken on the day of admission At the otological examination on June 4, the mucous membranes of the nose appeared normal, the pharynx slightly reddish. The ear-drums were dull, but not reddish. Their position was normal The mobility of the left ear drum was decreased About 0.1 ml of clear exudate was obtained by puncture of the left ear. RS virus was isolated from the exudate and from the throat swabs, as shown in Table 2 At the time of the puncture the patient was receiving antibiotics No bacteria were isolated from the exudate, and no pathogenic bacteria from the throat swab The exudate obtained from the right ear 7 days later was negative for virus and also for bacteria, although one of the throat swabs still contained some RS virus, as shown in Table 2. The RS virus antibody titer rose from <1/4 to 1/64

In this case RS virus was readily isolated from the middle ear exudate obtained 5 days after the beginning of the respiratory illness. However, no virus was isolated from the exudate obtained from the other ear 12 days after the beginning of the illness

Case No 6.—This 3-month old boy was hospitalized on June 3, 1965, for cough and breathing difficulties Initially he was exhausted, pale and slightly cyanotic The clinical and x-ray diagnosis was bronchopneumonia Ia At the otological examination carried out on June 4, the mucous membranes of the nose were slightly reddish, but not covered with exudate The ear-drums were pale and thin, and the reflex was visible The mobility of the left ear-drum was decreased About 0.1 ml of exudate was obtained by puncture of the left ear RS virus was isolated from the exudate and also from the throat swabs The exudate was negative for bacteria, and the throat swabs contained only bacteria normally present in the throat More detailed data on the case are given in the tables In spite of the antibiotic therapy initiated, the patient developed a bilateral, more pronounced middle ear infection with ballooning of the ear-drums This made puncture desirable, and on June 8 a thin exudate was obtained by puncture from both ears. These exudates were not cultured for viruses or bacteria However, a throat swab was taken on June 12, and this was still positive for RS virus

In this case RS virus was isolated, on the 5th day after the onset of symptoms, from the middle ear exudate of a 3 month-old child suffering from a severe illness of the lower respiratory tract Since the child developed a rather severe

middle ear infection in spite of the antibiotic treatment during the course of a virologically confirmed RS virus infection, the possibility cannot be excluded that RS virus was involved in the process which resulted in the aggravated ear symptoms

Children with no RS virus infection

This group consists of 17 children whose throat swabs were negative for RS virus and who on this account were considered not to be suffering from RS virus infection Nine of the children were over 12 months old and 11 attended the out patient department In the majority the symptoms and signs of middle ear infection were severe and the exudate obtained by puncture was mostly purulent or milky although in some cases serous or mucous and clear Aspiration puncture was performed bilaterally in 11 cases and unilaterally in 6 cases Neither RS virus nor other viruses were recovered from the middle ear exudates Bacterial species considered pathogenic for the middle ear however were isolated from the exudates of 11 (65%) of the children These bacteria were *Haemophilus influenzae Diplococcus pneumoniae* (type VI IX and XXXI) and *Neisseria catarrhalis* each species in 3 cases *Streptococcus pyogenes* in one case and *Streptococcus viridans* together with *Staphylococcus albus* in one case The exudates of 5 children were negative for bacteria and the exudate of one child contained *Staphylococcus albus* Most of the pathogenic bacteria (10 out of 11) which were found in the exudates were isolated from the children who visited the out patient clinic A pathogenic bacterium *Streptococcus pyogenes* was isolated from the exudate of only one child out of six who were treated on the wards However 5 of the 6 children in the wards were receiving antibiotics whereas only one out of 11 of the children from the out patient department was treated with antibiotics Throat swabs for bacterial examination were available from 15 children Pathogenic bacteria *Diplococcus pneumoniae type IX and Haemophilus influenzae respectively* were isolated from the throat swabs of 2 (2/15) of the children who also harboured these same bacteria in their middle ear exudates

One of the children aged 4 years 3 months who had *Haemophilus influenzae* in both middle ear exudates had a throat swab positive for herpes simplex virus but negative for pathogenic bacteria

Paired serum specimens which were only available for one child did not contain CF antibodies for RS virus or for the other respiratory viruses included in the test

DISCUSSION

Cases of otitis media due to proved virus infection have been reported by Zippel (1963) who described the histological changes in the middle ear in cases of hemorrhagic otitis media caused by influenza A virus Other cases of otitis media caused by the *influenza* virus have been re

genic bacteria. At the time of puncture the patient was receiving antibiotics. The titer of the first blood specimen, obtained 6 days after the puncture or 12 days after the beginning of the respiratory illness, was 1/32. The titer of the second blood specimen, obtained 2 weeks later, was also 1/32. Further data are given in Tables 1 and 2.

In this case RS virus was isolated from the middle ear exudate of both ears 5 days after the onset of a respiratory tract illness caused by RS virus. Since the middle ear infection which was associated with the RS virus infection was complicated by discharge from the ear, the possibility cannot be definitely excluded that RS virus was involved in the process which resulted in perforation of the ear-drum.

Case No. 3.—This 7-month-old boy was hospitalized on June 3, 1965, for cough and fever. The clinical and x-ray diagnosis was bronchopneumonia l.a. *Streptococcus pyogenes* was isolated from the throat swab taken on the day of admission. At the otological examination on June 4, the mucous membranes of the nose appeared normal, the pharynx slightly reddish. The ear-drums were dull, but not reddish. Their position was normal. The mobility of the left ear-drum was decreased. About 0.1 ml of clear exudate was obtained by puncture of the left ear. RS virus was isolated from the exudate and from the throat swabs, as shown in Table 2. At the time of the puncture the patient was receiving antibiotics. No bacteria were isolated from the exudate, and no pathogenic bacteria from the throat swab. The exudate obtained from the right ear 7 days later was negative for virus and also for bacteria, although one of the throat swabs still contained some RS virus, as shown in Table 2. The RS virus antibody titer rose from <1/4 to 1/64.

In this case RS virus was readily isolated from the middle ear exudate obtained 5 days after the beginning of the respiratory illness. However, no virus was isolated from the exudate obtained from the other ear 12 days after the beginning of the illness.

Case No. 6.—This 3-month old boy was hospitalized on June 3, 1965, for cough and breathing difficulties. Initially he was exhausted, pale and slightly cyanotic. The clinical and x-ray diagnosis was bronchopneumonia l.a. At the otological examination carried out on June 4, the mucous membranes of the nose were slightly reddish, but not covered with exudate. The ear-drums were pale and thin, and the reflex was visible. The mobility of the left ear-drum was decreased. About 0.1 ml of exudate was obtained by puncture of the left ear. RS virus was isolated from the exudate and also from the throat swabs. The exudate was negative for bacteria, and the throat swabs contained only bacteria normally present in the throat. More detailed data on the case are given in the tables. In spite of the antibiotic therapy initiated, the patient developed a bilateral, more pronounced middle ear infection with ballooning of the ear-drums. This made puncture desirable, and on June 8 a thin exudate was obtained by puncture from both ears. These exudates were not cultured for viruses or bacteria. However, a throat swab was taken on June 12, and this was still positive for RS virus.

In this case RS virus was isolated, on the 5th day after the onset of symptoms, from the middle ear exudate of a 3-month-old child suffering from a severe illness of the lower respiratory tract. Since the child developed a rather severe

were transmitted directly from the child to the cell cultures This method of RS virus inoculation has been shown to be effective by various investigators (Holzel *et al* 1963 Adams Thompson & Tobin 1963 Ross *et al* 1964) The U cells used for the purpose of isolation were sensitive to RS virus as concluded from the virus isolation results and the typical syncytial cytopathic effect of RS virus in these cells appeared to be prominent Furthermore since RS virus infections occur almost entirely in the form of epidemics it has to be pointed out that for successful isolations of RS virus from middle ear exudates this virus should be prevalent in the community

The paired sera of 7 children with RS virus isolations from throat swabs were tested for CF antibodies The RS virus antibody titers were found to be associated with the age of the children and with the time of collection of the serum specimens The 3 youngest children 3 months of age showed a slow development of antibodies and their convalescent serum titer never rose above 1/4 or 1/8 This corresponds to the observation of Chanock & Finlerg (1957) and Ross *et al* (1964) on the effect of age on the CF antibody response to RS virus and also to the observation of others (Berglund Vihma & Wickstrom 1965 Berglund Forssell & Harvo Noponen 1965) on the weak development of RS virus CF antibodies in children under 3 months of age The RS virus CF antibody responses of the rest of the children were in agreement with their somewhat higher age Thus 2 children 5 months and 7 months old showed a significant rise in the CF titer from <1 4 to 1/16 and to 1/64 respectively Two children 8 months and 10 months old already had CF antibodies to a titer of 1/32 in their first serum specimens However in both these cases the first serum specimen was obtained at a comparatively late stage of the disease

It is evident from the CF antibody titrations of the sera against other viruses that 3 children had an adenovirus infection and 1 child a cytomegalovirus infection in close association with or shortly after the RS virus infection This is not surprising in view of the observation (Berglund & Mantyjarvi 1966) that adenovirus infections were frequent and that infections caused by the cytomegalovirus also occurred among children of the same age living in the same town as those included in this study Since 3 of the children with RS virus isolations from their exudates and throat swabs did not respond with any increase of the antibody titer for adenovirus or cytomegalovirus during the course of the respiratory infection it appears unlikely that these 2 viruses could have caused middle ear affections in these 3 children Further studies now in progress may provide more information on such virus infections concomitant with the RS virus infection and possibly contributing to the occurrence of middle ear symptoms However the isolation of RS virus from the exudates of 9 children out of 10 with confirmed RS virus infection in this study strongly indicates that RS virus was the causative agent of the middle ear affections described

ported by Bellussi, Filippi & Scalfi (1959), who isolated influenza A viruses from bacteriologically sterile intratympanic exudates of patients with influenza and otitis Yoshie (1955) also isolated influenza A viruses from middle ear discharge of influenza otitis media No other reports on virus isolations from middle ear exudates have come to our attention One reason for the difficulty of isolating viruses from middle ear exudates might be the fact that middle ear punctures are usually carried out too late, when the middle ear infection originally caused by virus has already developed to a secondary bacterial infection The importance of taking the virus isolation specimens at an early stage of the respiratory disease is supported by the findings in the present study where, after the first successful isolations of RS virus from the middle ear exudates, subsequent isolations carried out on the same children during the later course of the RS virus infection were negative for RS virus The results of the present study also suggest that RS virus can readily be isolated from middle ear exudates of children not more than 12 months of age probably suffering from a primary infection The difficulty of isolating RS virus later in the course of the infection, and from older children (case No 10), presumably experiencing reinfection, might be explained by RS virus neutralizing antibodies in the exudate The presence in sterile otitis media exudates of neutralizing antibodies to viruses other than RS virus has been convincingly demonstrated by Surala, Tarpila & Halonen (1961)

In contrast to the situation in hemorrhagic otitis media caused by the influenza virus, the signs of RS virus middle ear infection were usually slight One sign always present was the decreased mobility of the eardrum revealed by the use of Siegle's pneumatic speculum This sign appeared to be due to the accumulation of exudate in the middle ear cavity Because of the scanty signs of infection one is tempted to ask whether there is a real RS virus infection of the middle ear epithelium, or whether the exudate containing virus has been formed elsewhere but brought to the middle ear mechanically from the nasopharynx by some mechanism, for instance swallowing However, the comparatively large amounts of exudate obtained by puncture, and the persistence of exudate in the middle ear cavity for a rather long time, up to 1 or 2 weeks, seem to indicate that the exudate really is formed within the middle ear

If there is a real RS virus infection of the middle ear epithelium, nothing can be postulated about the pathogenesis of this infection until the mode of the spread of the virus within the body is better known However, in view of the possibility of a viremic stage during the course of the RS virus infection, hematogenous spread of RS virus to the middle ear cannot be excluded, although spread per continuitatem from the nasopharynx would seem more plausible

In any case it appears that RS virus can be readily isolated from undiluted middle ear exudates of infants 12 months or younger suffering from RS virus infection In the present study the virus isolation specimens

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The results of the present study seem to indicate that infectious RS virus disappears earlier from the middle ear exudate than from the throat secretions. One reason for this might be a possible increase in the content of neutralizing antibodies in the exudate, taking place during the course of the infection. Another reason might be that the epithelial cells of the middle ear are more accessible than the other epithelial cells of the respiratory tract to the effect of interferon possibly formed in connection with the RS virus infection. Finally, it has to be borne in mind that the viruses encountered in the throat secretions are presumably derived from an epithelial surface much larger than that of the middle ear, and that for this reason RS virus might be present in a higher titer and accordingly easier to detect in the throat secretions than in the middle ear exudate

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We would like to express our gratitude to Prof Pekka Halonen, Prof John Wickstrom, Prof. Otto H Meurman and Dr. A. E Kortekangas, M D, for their many helpful suggestions and criticisms during the performance of this work We also would like to thank Miss Anja Pajasmaa, Mrs Leena Soini and Mrs Pirkko Lehtonen for their technical assistance.

ZUSAMMENFASSUNG

Proben von Exsudaten des Mittelohres wurden von Kindern wahrend einer Respiratory syncytial Virus Epidemie im Jahre 1965 in Turku, Finnland entnommen Die Exsudatproben wurden durch Punktion des Trommelfelles erhalten und auf Zellkulturen direkt verimpft Respiratory syncytial Virus wurde von dem einen Ohr oder beiden Ohren von 9 Kindern, 12 Monate alt oder jünger, isoliert Alle diese Kinder hatten eine Infektion des unteren Respirationstraktes, die der Respiratory syncytial Virus verursacht hatte, weswegen sie in die Klinik aufgenommen worden waren

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ACETYLCHOLINESTERASE ACTIVITY IN THE EFFERENT COCHLEAR FIBRES AFTER DESTRUCTION OF THE ORGAN OF CORTI AND AFFERENT FIBRES

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Prolonged acoustic trauma associated with neomycin sulphate treatment brought about the complete destruction of the organ and ganglion of Corti in a series of guinea pigs. Koelle and Friedenwald's test revealed the persistence of AChE activity in the intraganglionic spiral bundle but not on the basilar membrane, where Cajal-De Castro's silver impregnation method failed to disclose the presence of nerve fibres. Emphasis is laid on the different response displayed by the efferent and afferent fibres to the degenerative processes caused by the described treatment.

Acetylcholinesterase (AChE) activity has been observed in the organ of Corti in different animal species by Churchill, Schuknecht & Doran (1956), Vinnikov & Titova (1958), Kawamoto & Kaneko (1959), Schuknecht, Churchill & Doran (1959), Rossi (1960, 1962), Del Bo & Conti (1961), Conti (1961), Rossi & Cortesina (1962 *a*, *b*, 1963, 1965) and Hilding & Wersäll (1962). The site of this activity has been localized in the nerve of the efferent cochlear fibres, and this is in keeping with the finding that transection of the efferent cochlear fibres on the floor of the fourth ventricle results within a few days in the disappearance of AChE activity (Schuknecht, Churchill & Doran 1959, Rossi & Cortesina 1962 *a*, *b*, 1963, 1965, Smith & Rasmussen 1963) and of the highly granulated nerve endings found at the base of the inner and outer hair cells (Bairati & Iurato 1962, Iurato 1962, Kimura & Wersäll 1962, Spoendlin 1962, Smith & Rasmussen 1963, Spoendlin & Gacek 1963).

These efferent nerve endings exhibiting AChE activity form synaptic links with the receptor and afferent fibres. A synaptic linkage system is thus established between three components: receptor, afferent fibre and efferent fibre, but the functional role of this system is not fully understood.

The purpose of the present investigation was to study the behaviour of one of the components of this "threeway" linkage system, namely the efferent fibre, after destruction of the receptor and afferent fibre.

MATERIALS AND METHODS

Twenty male guinea pigs (*Cavia cobaya*) weighing between 300 and 400 g and reared under the same dietary and environmental conditions were used Destruction of the cochlear receptor and afferent fibres was achieved by treating the animals with neomycin sulphate (20 mg per kg per day subcutaneously) concurrently with traumatic acoustic stimulation (6144 Hz, 4096 Hz, 2048 Hz, 512 Hz 90 dB 8 hours daily) The experiment lasted 240 days altogether with four 60 day periods separated by three 30 day rest periods The acoustic trauma was effected with one of the above mentioned frequencies for each of the four periods of the experiment Eighteen months after completion of the experiment the animals were sacrificed

Since 11 animals died during the experiment the findings refer to only 9 animals (viz nos 3 4 7 12 14 15 18 19 and 20)

The animals were bled to death The petrosal portions of the temporal bones of guinea pigs 3 4 7 and 12 were decalcified with E D T A The right petrosal portion was embedded in paraffin and cut in serial sections parallel to the long axis of the cochlea The sections were then stained with hematoxylin and eosin The left petrosal portion was cut in the freezing microtome in sections perpendicular to the long axis of the cochlea which were then submitted to the Koelle and Friedenwald test (1949) for AChE The right petrosal portions of guinea pigs 14 15 18 19 and 20 were stained by Cajal De Castro s silver impregnation technique and serial sections made perpendicularly *to the long axis of the cochlea The left petrosal portions* were submitted to Koelle and Friedenwald s AChE test (1949) by the method described above

RESULTS

Examination of the serial sections of the petrosal portions embedded in paraffin and stained with hematoxylin and eosin showed that in 3 of the 4 animals (nos 3 4 and 12) the treatment had destroyed the organ of Corti at all levels of the cochlear duct and Corti s ganglion over the entire length of Rosenthal s canal In the fourth animal (no 7) destruction was not complete signs of degeneration were seen sparsely in second and apical turns of the cochlea

In the guinea pigs in which the organ of Corti appeared to be completely destroyed Koelle and Friedenwald s AChE test (1949) revealed no evidence of enzymatic activity in the cochlear duct By contrast AChE activity was demonstrated clearly *in the* intraganglionic spiral bundle and within the canaliculi of the osseous spiral lamina (Fig 1 A and B)

In guinea pig no 7 in which only partial destruction of the organ of Corti was obtained the Koelle and Friedenwald test disclosed two areas of

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organ and ganglion of Corti in all the coils of the cochlea The illustrative material presented by Fernandez (1951) and by Portmann (1952), who conducted experiments employing only prolonged acoustic stimulation and the findings of previous personal studies (Rossi & Olivieri 1958), entailing the use of neomycin sulphate alone, testify to the inability of each of these methods used independently, to cause the complete destruction of the organ and ganglion of Corti Even when used in conjunction in the present experiment, they were successful in only 6 out of 9 cases, probably because of individual variability in the degree of sensitivity to acoustic trauma and neomycin treatment

The findings of the present investigation show that the complete destruction of the organ of Corti results in (*a*) the disappearance of all AChE activity in the cochlear duct (*b*) the persistence of AChE activity in the intraganglionic spiral bundle, and (*c*) the survival of no nerve fibres beyond the habenula perforata When the experimental method failed to destroy the organ of Corti completely, histologic examination showed, (*d*) AChE activity in the cochlear duct and the intraganglionic spiral bundle, and (*e*) nerve fibres also beyond the habenula perforata

These findings are in keeping with those reported by Marco & Esteban (1964) Their contrast with the findings of Schuknecht Churchill & Doran (1959), who demonstrated the persistence of AChE activity in the cochlear ducts of cats sacrificed within twenty days of introducing streptomycin into the bulla, is more apparent than real In Fig 7 of their paper we see that at the site of the outer hair cells where the destructive process seems to have been complete there is far less AChE activity than at the inner hair cells which seem to be at least partially preserved This suggests that the experiment was of too short duration to allow of total destruction of the organ of Corti

Nor do our findings conflict essentially with those of Spoendlin (1958 1962) or Duvall & Wersall (1964) The latter refer to the integrity of all the nerve endings, while Spoendlin (1958 1962) only mentions the presence of highly enlarged swollen mitochondria in the nerve endings at the base of the outer hair cells without describing the features or defining the nature of these endings Spoendlin (1958 1962) conducted his experiments on guinea pigs subjecting them to acoustic trauma Duvall & Wersäll (1964) used streptomycin in the same species of animal But in neither case did the technique employed (very different from ours) succeed in destroying the organ of Corti As regards nerve endings our findings are to a certain extent comparable to those reported by Engstrom & Kohonen (1965)

It should be remembered that in contrast to the situation with all other neurons of the nervous system transection of the central process of a cell of Corti s ganglion brings about the complete irreversible degeneration of all the parts of the neuron (Schuknecht & Woellner 1955, Spoendlin & Gacek 1963), with the exception of the endings linked synaptically with



Fig. 1. (*A*) Guinea pig no. 12. First turn of right cochlea. Organ and ganglion of Corti are destroyed, while the intraganglionic spiral bundle has survived (*arrow*). Hematoxylin and eosin. ×65. (*B*) Guinea pig no. 12. First turn of left cochlea. Following destruction of the organ and ganglion of Corti, the Koelle and Friedenwald test demonstrates the presence of AChE only in the intraganglionic spiral bundle. Koelle and Friedenwald. ×60. (*C*) Guinea pig no. 7. First turn of left cochlea. Persistence of acetylcholinesterase activity at the inner and outer hair cells. Koelle and Friedenwald. ×60. (*D*) Guinea pig no. 4. Ampullary crest of the left labyrinth. Intense acetylcholinesterase activity is seen in the neuroepithelium and related nerve fibres. Koelle and Frieden-wald, ×60.

AChE activity, corresponding presumably to the inner and outer hair cells (Fig. 1 C).

Examination of the petrosal portions submitted to Cajal–De Castro's silver impregnation revealed, in animals 14 and 19, a large number of surviving neurons of Corti's ganglion, whereas in animals 15, 18 and 20 the neurons of Corti's ganglion were found to have been destroyed. In these three animals, nerve fibres were seen in the osseous spiral lamina but not on the basilar membrane.

In guinea-pigs 14 and 19 AChE activity was demonstrated in the organ of Corti but no AChE activity remained in guinea-pigs 15, 18 and 20, in which the organ of Corti had been destroyed.

In none of the animals were degenerative phenomena seen in the neuroepithelium of the ampullary crests or maculae; in all the animals these structures exhibited AChE activity (Fig. 1 D).

COMMENT AND CONCLUSIONS

In the present investigation neomycin treatment was combined with long-term acoustic trauma in order to cause complete destruction of the

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the hair cells (Spoendlin & Gacek, 1963). These writers maintain that the peripheral endings of the dendrite are closely related metabolically with the supporting cells. And indeed, retrograde degeneration of the afferent neuron, which results from acoustic trauma or antibiotic poisoning, is seen only when the supporting cells are damaged (Spoendlin & Gacek, 1963).

Transection of the efferent axon, on the other hand, causes complete, irreversible degeneration as far as the endings (Bairati & Iurato, 1962; Kimura & Wersäll, 1962; Spoendlin, 1962; Smith & Rasmussen, 1963; Spoendlin & Gacek, 1963), which therefore *would appear to be unrelated* metabolically to the supporting cells of the organ of Corti.

Briefly, then, the findings of the present investigation show that the disappearance of AChE activity on the basilar membrane following destruction of the organ and ganglion of Corti is commensurate with the destruction of the terminal portion of the efferent fibres, which, even after many months, exhibit no signs of regeneration.

RÉSUMÉ

En soumettant un groupe de cobayes à un traumatisme acoustique chronique associé à un traitement prolongé avec du sulfate de néomycine, les auteurs ont provoqué la destruction complète de l'organe et du ganglion de Corti. Ils ont constaté chez ces cobayes la persistance de la positivité à la réaction de Koelle et Friedenwald pour l'ACHE en correspondance du faisceau spiral intraganglionnaire, tandis que cette activité enzymatique avait disparu au niveau de la membrane basilaire où, à l'aide de la méthode de Cajal-De Castro à l'imprégnation d'argent, ils n'ont plus observé la présence de fibres nerveuses. Ils soulignent le comportement différent des fibres efférentes et des fibres afférentes par rapport aux processus dégénératifs provoqués par le traitement employé au cours de ces expériences.

ZUSAMMENFASSUNG

Die Verfasser unterzogen eine Gruppe Meerschweinchen einem chronischen akustischen Trauma sowie einer längeren Behandlung mit Neomycinsulfat und verursachten somit die vollständige Zerstörung des Cortischen Organs und des Ganglion spirale cochlea. Bei diesen Versuchstieren stellten sie die Positivitätsfortdauer zur Koelle und Friedenwaldschen Reaktion für das ACHE auf Höhe des spiralförmigen intraganglionären Bündels fest, während diese Enzymtätigkeit auf Höhe der Basilarmembran nicht beobachtet wurde, wo mit Hilfe der Cajal-De Castro-Methode unter Silberimprägnation keine Nervenfaser mehr aufzufinden waren. Sie unterstreichen das verschiedentliche Verhalten der efferenten im Vergleich mit den afferenten Fasern gegenüber den durch diese Behandlung verursachten Degenerationsprozessen.

THE PHYSICAL PARAMETERS OF COUGH: THE LARYNX IN A NORMAL SINGLE COUGH

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Simultaneous recordings of flow rate, air volume, subglottic pressure and acoustic signal were performed on single normal coughs of healthy subjects. Sequential changes in resistance at the level of the larynx and in power at the subglottic level were traced by reference to these measured parameters. Successive phases were classified according to specific dynamic actions. Mean and standard deviations of critical measurements and their correlation matrix were obtained with electric computors.

The resulting information indicates that the traditional description of inspiration, compression and expiration represents only a superficial image of an extremely complicated transient phenomenon. Detailed observations of the physical parameters reveal important physiologic patterns. Laryngeal control of the power and resistance appears of paramount importance for the production of an effective cough. The secondary augmentation of resistance discourages re-entry of the expelled substance.

The results of this investigation provide normal aerodynamic standards for comparative studies of various human coughs.

The act of coughing is an indispensable mechanism for the expulsion of secretions and foreign bodies from the lower respiratory tract. Both clinicians and scientists are familiar with the major stages of a cough: (1) the initial inspiration, (2) the tight closure of the glottis with compression of air in the lower respiratory tract, and (3) the sudden expulsion of air through the glottis. Various physiologic aspects of cough have been observed with endoscopic, radiologic, photographic, or electromyographic techniques. However, little is known about the sequential changes of the physical parameters which are specific for this event, such as the air flow, the subglottic pressure, and the sound of cough. Attempts have been reported to analyze the aerodynamics of cough from studies of the tracheobronchial movements (Bucher, 1958, Ross, Gramiak & Rahn, 1955) but the published information regarding its physical mechanism is quite lim-

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born 568 100) for photographic registration In order to detect the rapid transitory changes in each parameter, the recording speed was set at 25 mm/sec, which permitted a satisfactory visual presentation of the measurements

The accuracy of these measurements was affected by the attenuation of the amplified signals and the recording speed In the measurement of the flow rate and subglottic pressure, 0 05 l/sec and 1 0 cm H_2O proved the smallest reliable units In the time measurements, 0 02 sec represented the limit of reliability

During the experiment the subject was asked to produce a single gentle cough in a natural manner while holding the mask air tight The recorded graphs were inspected carefully and all imperfect samples were eliminated As a result, we obtained eight measurable samples from subjects 1 and 2, six from subject 3, five from subject 4, and four from subject 5 respectively

MEASUREMENTS

Before attempting a quantitative description of the aerodynamic properties of cough, qualitative studies are necessary in order to appreciate the significance of the measured physical parameters Representative recordings and their related schematic drawings are presented in Fig 1 As is shown by these graphs, the aerodynamic pattern of a cough is clearly divided into three fundamental phases Thus the air flow demonstrates a negative flow phase, a minimum flow phase, and a positive flow phase Parallel to these findings, the subglottic pressure indicates a negative pressure phase, a rapid rise, and a positive pressure phase Roughly speaking, these three fundamental phases correspond to each initial inspiration, tight closure of the glottis, and to the explosive expiration Evidently the expectorant action is accomplished during the positive flow and positive pressure phase A vigorous movement of the whole respiratory system takes place during this positive phase, as a result, the aerodynamic pattern shows a complex picture

Three subordinate phases can be distinguished during the *positive flow phase* Phase A is characterized by an abrupt and almost linear augmentation of the flow rate After reaching its peak at the completion of phase A, the flow rate decreases rapidly This peak is designated as maximum flow rate peak throughout this paper, and the rapid decrease in the flow rate is described as phase B Following the vigorous excursion indicated by phases A and B, the flow rate returns to the zero level in a rather gentle manner during phase C

The subglottic pressure also shows considerable gyrations during the *positive pressure phase* The maximum elevation of the subglottic pressure also occurs at the termination of a steep rise, and this phase is followed by a sharp decrease in pressure After the decline reaches a certain level, the pressure gradient continues in one of two directions In one type,

ited This lack of factual knowledge has led to contradictory opinions about the participation of the larynx in this physiologic process

In order to establish the physical properties of a cough and the significance of laryngeal participation, a series of experiments have been performed at our laboratory. This report presents a detailed description of the normal aerodynamic events in a single gentle cough at the level of the larynx Subsequent accounts will describe our results in a series of coughs, and in subjects with diseases of the larynx or disorders of function

TECHNIQUE OF INVESTIGATION

Simultaneous recordings of the subglottic pressure, the flow rate (or volume velocity), the volume of air (inspired or expired), and the sound wave of a cough were obtained from five normal subjects Our subjects varied in age from nineteen to twenty-three years; three subjects were male and two were female A thorough history indicated no significant illnesses, and the normal appearance and function of the larynx were confirmed by indirect laryngoscopy. Respiratory function tests were carried out before each experiment, using a spirometer of the Benedict Roth type The subjects demonstrated vital capacities of about 110% of the values derived from Baldwin's formulae

Under local anesthesia, a guarded 18 gauge needle with removable stylus was introduced into the trachea 2 or 3 cm below the cricoid cartilage The subglottic pressure was transmitted via a plastic tube to a pressure transducer (Sanborn 267 A) This transducer has linear characteristics ranging from 100 mm Hg to 400 mm Hg under normal atmospheric conditions To prevent excessive movements of the needle during successive coughs, one of us maintained manual control throughout the experiment

A pneumotachograph was used for the recording of the flow rate This equipment consists of (1) a respiratory mask, (2) a laminar flow resistor composed of a 400 mesh morel wire screen 20 5 cm² in area, (3) a bidirectional differential gas pressure transducer (Sanborn 270), and (4) a carrier preamplifier (Sanborn 350-1100 B) The pneumotachograph had been calibrated by a rotameter with an accuracy of 1 0% at maximum flow rate The rise time of the differential pressure transducer was set within 5 milliseconds During cough, the flow rate varied greatly, in a few cases the peak reached momentarily more than 10 liters per sec The attenuation range was carefully selected for each case in order to record the precise peak value and avoid excessive deviations of the curve

The volume of air was calculated from the flow rate by an integrating preamplifier (Sanborn 350-3700) The cough sound was picked up by a uni-directional condenser microphone 30 cm from the outlet of the pneumotachograph and recorded on a dual channel tape recorder (Sony 777)

The four parameters—subglottic pressure, flow rate, air volume, and sound were transmitted to four channels of a poly beam recorder (San-

variety the subglottic pressure decreases sharply after the first peak and then gradually levels off to zero without showing a second rise (Fig 1 *b*) Among our five subjects four demonstrated a double peak, the six coughs of subject 3 presented a single pressure peak

We have noted a consistent time lag between the first pressure peak and the maximum flow rate peak, the latter occurs after the fall in pressure has already started There is also a very small time interval between the first pressure peak and the initiation of the flow rate increment, in most cases the flow rate begins its steep climb, before the peak pressure is reached

The measurements of the different physical parameters were recorded as follows time in seconds, pressure in cm of water, flow rate in liters/sec, and volume of air in liters The measured factors consisted of (1) the duration of each phase and the time lag between the first pressure peak and the maximum flow rate, (2) the lowest pressure in the negative pressure phase, (3) in the positive pressure phase the first peak pressure, the pressure corresponding to the point of maximum flow rate at the termination of phase A the second peak pressure and the lowest point pressure in phase B, and the pressure at the beginning of phase C (4) the maximum flow rate in the negative flow phase, (5) in the positive flow phase flow rate peak and the flow rate at each other point where the pressure was measured, and (6) the volume of inspired and expired air From these measurements, the power and resistance were calculated at each critical moment The resistance at the level of the larynx was expressed by the ratio of the subglottic pressure and the flow rate in cm H_2O/l sec The power at the subglottic level was defined as the product of the flow rate and the subglottic pressure in cm $H_2O \times 1$/sec

As a result thirty three variables were obtained for each cough from each subject The mean value, the standard deviation, and the coefficient matrix or these thirty three variables were calculated, employing an electronic computer (The electronic computation was performed on the I B M computer model 7040 and 7094, in the Computing Facility of the Center for Health Sciences at U C L A)

RESULTS

1 *Duration of the various phases of cough*

Table 1 records the mean, maximum and minimum values and the standard deviations for the negative flow phase and the positive flow phase of each subject The most conspicuous finding is the duration of the minimum flow phase which remains remarkably consistent in all subjects Individual differences in the mean and standard deviations are quite insignificant in this phase On the other hand the widest variability in time is noted in the negative flow phase a significant correlation is apparent between the duration of this phase and the volume of air inspired

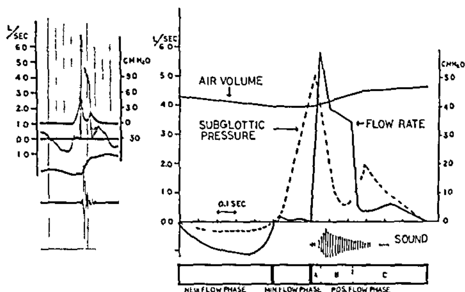


Fig 1a

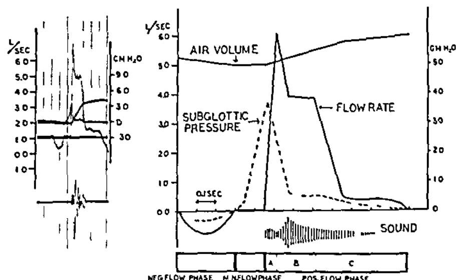


Fig 1b

Fig 1 Simultaneous recordings of flow rate, volume of air, subglottic pressure and acoustic signal in two single coughs The corresponding schematic drawings demonstrate the three fundamental phases of a cough and the three subordinate phases in the positive flow phase Figure 1 *a* represents an example of three subglottic pressure peaks in the positive pressure phase figure 1 *b* indicates only one sharp peak in the positive pressure phase

the pressure rises again temporarily, and then gradually decreases to the zero level (Fig 1 *a*) The second peak is less prominent than the first and is usually located close to the termination of phase B, the lowest point of this episode is noted near the middle of phase B In this type, therefore, we observe three extremes which we have designated as first peak pressure, lowest point pressure, and second peak pressure By contrast, in the other

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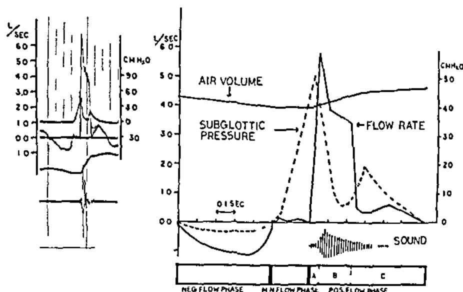


Fig 1 a

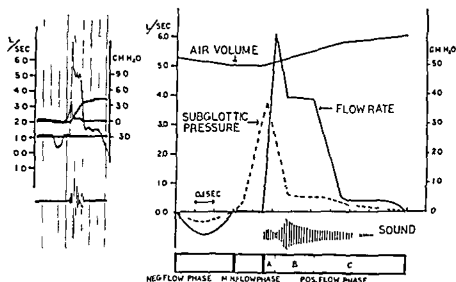


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TABLE 3 *Volume (in liters) of inspired and expired air Maximum inspiratory, and maximum expiratory flow rate (in liters/second)*

Note differences between male and female subjects * indicates female subjects

	Vol inspired				Max insp flow rate				Vol expired				Max exp flow rate			
Subj	Mean	Max	Min	S D	Mean	Max	Min	S D	Mean	Max	Min	S D	Mean	Max	Min	S D
1	0 49	1 20	0 05	0 43	0 78	1 15	0 20	0 38	1 02	1 35	0 55	0 33	5 05	6 40	3 25	1 02
2	0 50	1 10	0 16	0 32	0 78	1 30	0 40	0 29	1 06	1 50	0 70	0 36	6 19	7 62	4 70	1 13
3	0 53	1 30	0 20	0 41	1 12	2 70	0 60	0 80	1 25	1 55	0 90	0 29	5 07	6 12	4 00	0 03
4	0 09	0 15	0 05	0 01	0 24	0 55	0 10	0 19	0 54	0 85	0 30	0 22	3 33	4 45	2 65	0 82
5	0 35	0 80	0 05	0 32	0 32	0 95	0 10	0 42	0 60	0 75	0 30	0 21	3 26	3 95	2 35	0 69

rate peak and the first subglottic pressure peak This time lag measures approximately 0 03 sec, its length is linked to the duration of phase A The correlation coefficients in subjects 1, 2, 3 and 5 are 0 86, 0 84, 0 86 and 0 92 respectively

2 *Volume of inspired and expired air, and maximum inspiratory and expiratory flow rate*

The mean, maximum and minimum values, and the standard deviations of these four factors are given in Table 3 This table demonstrates a remarkable difference between the values obtained in male and female subjects For example, the volume of air expired during a single cough in the male subjects was about 1 0 l while in the female subjects it was approximately one half of this amount It is also interesting that both volume and flow rate vary considerably from subject to subject, with large standard deviations Generally speaking the volume of inspired air, and the maximum inspiratory and expiratory flow rates measure 0 5 l, 0 8 l/sec, and 5 5 l/sec in the male subjects and 0 2 l, 0 3 l/sec, and 3 3 l/sec in the female subjects

3 *Inspiratory peak pressure, first peak pressure, pressure at maximum flow rate peak, lowest point pressure and second peak pressure*

The information on the subglottic pressure at these critical points is summarized in Table 4 As we mentioned previously, two different subglottic pressure patterns were observed in the positive pressure phase One type showed two upper and one lower pressure peak, while the other pattern produced only one upward peak The six coughs of subject 3 belonged to this latter configuration, in Table 4, therefore, no values are recorded for the lowest pressure, and the second peak pressure in this case In the same subject we note that the first peak pressure and the pressure corresponding to the point of maximum flow rate are conspicuously lower than those of the subjects

TABLE 1 *Duration (in seconds) of three fundamental phases negative flow phase, minimum flow phase, and positive flow phase*

Subj	Neg flow phase				Min flow phase				Pos flow phase			
	Mean	Max	Min	S D	Mean	Max	Min	S D	Mean	Max	Min	S D
1	0.93	1.48	0.60	0.36	0.15	0.24	0.09	0.05	0.60	0.86	0.42	0.13
2	1.00	1.98	0.62	0.50	0.15	0.19	0.10	0.01	0.67	0.86	0.50	0.12
3	0.64	1.00	0.36	0.26	0.15	0.18	0.12	0.02	0.83	1.26	0.62	0.22
4	0.76	1.30	0.44	0.33	0.17	0.13	0.18	0.05	0.54	0.65	0.42	0.10
5	0.45	0.84	0.32	0.27	0.22	0.34	0.17	0.08	0.76	1.10	0.40	0.28

The correlation coefficients between these findings are 0.66, 0.92, and 0.90 in subjects 1, 2 and 3 respectively.

In the positive flow phase, we observe the small differences in duration ranging from 0.54 to 0.83 sec, but a significant variability is indicated in different subjects by the relatively large standard deviation in each individual. As mentioned previously, the characteristics of the flow rate pattern suggest a further division of this phase into three subsections. Information on the duration of these three sub phases A, B and C, is presented in Table 2. The mean duration of phase A ranges from 0.051 to 0.078 sec, phase B from 0.15 to 0.36 sec, and phase C from 0.29 to 0.50 sec. It appears that phase A and phase B show a remarkably constant time pattern, while phase C demonstrates a comparatively wide divergence in time. We also find a very high correlation between the length of the entire positive flow phase and sub phase C. This observation indicates that individual *variations in the duration of the positive flow phase* depend mainly on the length of phase C, whereas phase A and B remain relatively constant. The correlation coefficients between the duration of sub phase C and the positive flow phase are 0.99, 0.98, 0.97, 0.92 and 0.99 in subjects 1, 2, 3, 4 and 5 respectively.

As noted, there was a consistent time lag between the maximum flow

TABLE 2 *Duration (in seconds) of phases A, B, and C, and of time lag between maximum flow rate peak and first subglottic pressure peak*

Subj	Phase A				Phase B				Phase C				Time lag			
	Mean	Max	Min	S D	Mean	Max	Min	S D	Mean	Max	Min	S D	Mean	Max	Min	S D
1	0.051	0.070	0.030	0.014	0.21	0.24	0.16	0.024	0.33	0.54	0.20	0.13	0.039	0.060	0.030	0.010
2	0.038	0.050	0.020	0.009	0.24	0.26	0.17	0.026	0.40	0.56	0.24	0.11	0.032	0.040	0.020	0.006
3	0.048	0.060	0.040	0.010	0.36	0.40	0.32	0.037	0.43	0.82	0.16	0.21	0.031	0.040	0.020	0.009
4	0.090	0.100	0.070	0.012	0.15	0.22	0.13	0.035	0.29	0.42	0.16	0.11	0.041	0.060	0.020	0.018
5	0.078	0.100	0.050	0.021	0.17	0.18	0.16	1.011	0.50	0.17	0.84	0.27	0.042	0.060	0.010	0.023

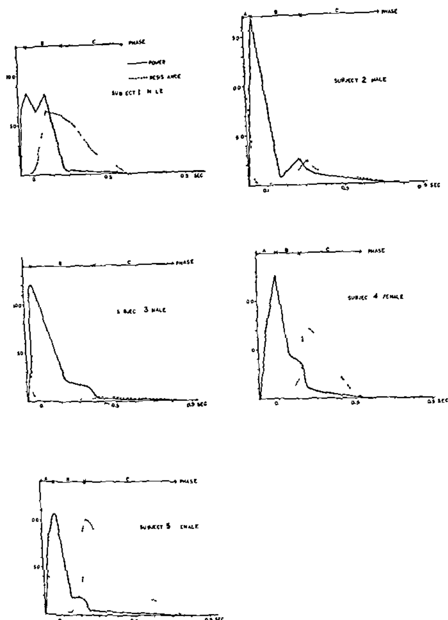


FIG 2 Sequential changes in the power and resistance throughout a typical single cough burst in 5 different subjects Solid line demonstrates changes in power dotted line changes in resistance Horizontal axis shows time in seconds vertical axis power in cm $H_2O \times l/sec$ and resistance in cm $H_2O/l/sec$ Except for subject 3 power and resistance phases are readily distinguished

TABLE 4 *Pressure recordings (in cmH_2O) negative peak pressure, first peak pressure, pressure at maximum flow rate peak, lowest point pressure, and second peak pressure.*

Subj	Neg peak pressure				First peak pressure				Press at max flow rate peak			
	Mean	Max	Min	S D	Mean	Max	Min	S D	Mean	Max	Min	S D
1	1 76	3 16	0 60	1 17	56 0	68 0	31 9	11 6	45 1	55 4	18 9	12 1
2	2 10	3 00	1 20	0 73	51 7	72 0	35 7	9 6	26 9	28 5	15 0	8 3
3	1 35	3 00	0 C0	0 91	41 0	60 5	22 5	13 3	21 4	31 5	13 5	7 3
4	4 51	8 50	3 00	2 30	52 3	63 7	42 5	9 7	36 2	53 2	30 0	9 9
5	4 13	6 00	1 50	2 30	17 4	51 0	39 0	6 1	33 0	40 5	28 0	5 8

Subj	Lowest point pressure				Second peak pressure			
	Mean	Max	Min	S D	Mean	Max	Min	S D
1	31 4	38 0	6 3	11 3	42 2	60 2	22 5	14 1
2	2 2	4 9	1 0	1 2	20 1	28 5	16 3	3 10
4	19 0	27 8	9 0	7,0	27 8	33 0	22 5	2 9
5	8 2	13 5	4 5	4 3	21 9	25 8	19 5	2 7

Except for subject 3, the first peak pressure at the termination of the rapid rise phase A measures about 50 cm H_O However, considerable individual variability is indicated by the large standard deviation Subsequently, the pressure pattern shows even greater subject to subject variation, especially in the mean values of the lowest point pressure where we observe a wide divergence from 2 2 to 34 4 cm H_2O The sex linked difference observed in the air flow data is not duplicated in the pressure pattern

4 *Power and resistance at the level of the larynx during cough*

In computing these factors, power and resistance were determined at every critical point for each cough, then the average power and resistance at these points were obtained for each subject *The sequential changes in* the power and resistance can be traced by referring to these mean values and their relation to time Fig 2 demonstrates the correlation between sequential changes in the power and resistance throughout each cough burst Except for subject 3, the graphs present close similarities in the following respects·

(*a*) Maximum *power* is attained at the terminal point of phase A corresponding to the maximum flow rate peak Thereafter the power decreases rapidly until the end of phase B, with a slight reversal or retardation during the mid portion In phase C, this steep fall in power gradually levels off until it reaches zero

(*b*) The *resistance*, on the other hand, decreases during phase A and during the initial half of period B The lowest point of the resistance cor-

DISCUSSION

A cough can occur as a single explosion, or as a series of several bursts, it may be gentle or violent in intensity, it can be initiated voluntarily or involuntarily Further differentiation is possible between a cough produced by a normal subject and that produced by a patient with a respiratory ailment In order to understand the underlying physiologic mechanisms in these widely varying phenomena, the exploration of a single cough produced normally by a healthy individual becomes of primary significance Previous investigations concentrated mainly on the lower respiratory structures without due attention to the function of the larynx It was the goal of the present study to obtain detailed information concerning the aerodynamic mechanism of a cough and to re evaluate the participation of the larynx in this event

Our investigations indicate that the aerodynamic process during a single cough is not a simple action but rather a complex and rapidly changing phenomenon Variations can be recognized from person to person, and even in the same subject However, we have observed that certain specific physical activities occur during each cough, activities which provide an effective mechanism for the protective and expectorant purpose of this vital physiologic event

The acknowledged major components of a cough consist of three stages (1) A deep initial inspiration, (2) the compression of air in the lungs and tracheobroncheal tree by the forceful contraction of the expiratory muscles and by the tight closure of the glottis, and (3) a sudden explosive expiration Aerodynamically, these three major stages can be expressed in terms of air flow rate and air pressure The air flow pattern is divided into a negative flow phase, a minimum flow phase, and a positive flow phase, the subglottic pressure pattern into a negative pressure phase, a rapid rise phase, and a positive pressure phase, in accordance with their dynamic behavior

There is general agreement that the expulsion of air under high velocity is essential for the production of sufficient power for the elimination of foreign bodies or other pathologic products from the lower respiratory passages Bucher (1958) postulates that active expiratory forces are necessary for this increase in the velocity of the expiratory air flow—the elastic power of the lungs and thorax and/or the forceful contraction of the expiratory muscles In our opinion, this observation is correct to the extent that greater volume velocity produces greater power

In addition we suggest that an increase in pressure is equally important for the production of additional power Moreover, the elimination of a foreign body cannot be accomplished effectively while the resistance at the level of larynx remains high An effective cough, therefore, necessitates adjustments which provide both higher power and lower resistance Our

TABLE 5 *Significant correlations between time, volume of air, flow rate, and subglottic pressure*

	S 1	S 2	S 3	S 4	S 5
(1) *Coefficient of correlation between volume inspired and*					
Duration of neg phase	0 66	0 92	0 90		
Vol expired	0 83	0 63	0 90	0 70	
Max flow rate	0 77	0 71		0 89	
Max power		0 60		0 92	0 66
(2) *Coefficient of correlation between volume expired and*					
Vol inspired	0 83	0 63	0 90	0 70	
Max flow rate	0 89	0 89	0 86	0 82	0 97
Max power	0 72	0 62	0 72	0 75	
(3) *Coefficient of correlation between max flow rate and*					
Vol inspired	0 77	0 71		0 98	
Vol expired	0 89	0 89	0 86	0 82	0 97
First press peak	0 69			0 89	0 81
Max power	0 88	0 70		0 91	
(4) *Coefficient of correlation between first pressure peak and*					
Vol expired	0 70			0 89	0 83
Max flow rate	0 87	0 75		0 77	0 87
Max power	0 97	0 81		0 74	

responds to the lowest pressure point, where the graph reverses its direction The increment in resistance continues to a peak which is located near the end of phase B During phase C, the resistance falls gradually to the zero level

In summary, in 4 of our 5 subjects the factor of power is dominant during phase A and the initial half of phase B, and the resistance assumes more importance during the last half of phase B and during phase C In subject 3, the sequential changes in power show a close resemblance to these findings, however, the significance of the resistance is less pronounced

5 *Significant correlations between time volume of air flow rate and subglottic pressure*

The correlation matrix of thirty-three measured items suggests that the various physical parameters of a cough bear a close and complex relation to each other Our selection has been limited to those factors which appear significant by their high correlation Table 5 demonstrates this significant correlation between the volume of inspired and expired air, the maximum flow rate, and the first peak pressure as related to the maximum power.

DISCUSSION

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investigation proves that in the airway the larynx regulates this balance of power and resistance in an extremely efficient and skilful manner This regulatory function is undoubtedly one of the most significant contributions of the larynx

Our studies further demonstrate an increase in the resistance at the level of the larynx after sufficient power has been attained We believe that this augmentation of resistance represents a second important contribution of the larynx to a cough The power is unquestionably required for the elimination of a foreign substance We presume that the subsequent increase in the resistance protects the lower respiratory passages from reinvasion by the foreign substance

These considerations lead to the conclusion that most normal coughs have two distinctive physical phases During the initial stage of the positive flow phase, the whole expiratory system concentrates on attaining maximum power for the expectorant action in which the larynx participates to a significant degree Subsequently the larynx provides resistance to the air flow in order to prevent a reinvasion by the expelled substance

We can describe the movements of the laryngeal structures during the positive flow phase on the basis of this aerodynamic mechanism During phase A, the glottis widens to its maximum extent in order to provide a minimum of resistance Near the middle of phase B, when this purpose has been achieved, the glottis narrows again in order to provide the needed resistance

Pressman & Kelemen (1955) report that in many instances the forceful wide opening of the larynx is followed by a reaction in which the true vocal cords rebound momentarily almost to the median line before they resume their neutral respiratory position During his animal experiments, Floersheim (1959) discovered that the glottal movements during a cough comprise three different stages, a narrowing, a widening and another narrowing The first narrowing was observed during the inspiratory period, while the movements during the expiratory phase consisted of both widening and narrowing, this information concurs with the results of our investigations on human subjects The high speed cinematographic observations of Isshiki & von Leden (1963 and 1965) indicate a contraction of the supraglottic structures, principally the epiglottis and ary-epiglottic folds, while the glottis reaches its maximum opening The authors explain these findings by the effect of the rapid air current upon the surrounding structures, the Bernoulli phenomenon

On the basis of these investigations, the glottal movements during the expiratory period can be summarized as follows (1) All laryngeal structures are set in motion during a cough, (2) following the tight closure of the glottis, the larynx opens and provides a free passage during the initial phase of the explosive expiratory period, (3) thereafter, the glottis narrows before the laryngeal structures gradually return to their normal inspiratory position

The power of the expulsion, the resistance of the glottis, and the movements of the laryngeal structures affect the physical parameters of the cough An understanding of this aerodynamic process calls for a discussion of the various physical parameters

The aerodynamic equivalents of *the initial inspiratory phase are represented* by the negative flow phase and by the negative pressure phase because these activities occur at the same time The succeeding phases of minimum air flow and rapid pressure rise also develop simultaneously The length of the negative flow phase, which shows such variability, proves correlated with the volume of air inspired The smaller the volume of the inspired air the shorter is the duration of this phase, and vice versa The length of the minimum flow phase is less variable and in the case of a gentle single cough measures about 0 17 sec Apparently this phase corresponds to the stage of firm glottic closure While it is generally assumed that there is no air flow at all during this period, our experiments indicate a small leak of air at the beginning of this phase This phenomenon may *be attributable to the escape of some air before the completion of the force*ful closure

During the rapid rise phase, the subglottic pressure builds up to its peak We have been impressed by the constant time lag between the terminations of the minimum flow phase and of the rapid rise phase The rise in pressure continues beyond the termination of the minimum flow phase and ends before the maximum flow rate is attained This finding indicates that the subglottic pressure increases even after the glottis opens and the expiratory air begins to escape This time interval between the glottal opening and the subglottic pressure peak was also demonstrated by Floersheim (1959) during his animal experiments

Whittenberger & Mead (1952) observed in their investigations on human subjects that the intrapleural pressure monitored by an esophageal balloon continues to rise momentarily after the glottis opens The authors suggest that the expiratory muscular effort is even greater after the release than before the glottic opening According to our measurements, this time lag measures about 0 03 sec In this connection, Cherniack's (1961) description of the cough reflex is of interest "After the thoracic pressure has reached a very high level, the glottis suddenly opens slightly Since the intra abdominal pressure is now higher than the intra-thoracic pressure the diaphragm is pushed up during a violent explosive movement of air from the lower to the upper respiratory tract" The time lag between the pressure peak and the opening of the glottis may well be attributed to this elevation of the diaphragm which in turn may be induced by a slight opening of the glottis

Regarding the opening of the glottis, high speed cinematographic studies (Isshiki & von Leden, 1963 and 1965) reveal that the first opening of the glottis occurs at or near the antero-posterior mid point, and that the amplitude of vibration increases symmetrically and rapidly cycle by cycle

This vibratory period presumably corresponds to the time lag in question

Among the subordinate three phases during the positive flow phase, phase A and B demonstrate a remarkably consistent relationship in time, while the duration of phase C shows a somewhat larger variation The mean duration of phase A, B, and C are 0 061, 0 23, and 0 41 sec respectively. The high correlation coefficient between the duration of the positive flow phase and that of phase C indicates the dependence of the former upon the latter, since phase A and phase B show relatively little change

In the volume of inspired and expired air, there is a remarkable difference between male and female subjects The mean value of the inspired air volume measures 0 5 l in the male and 0.2 l in the female subject, while the expired air volume averages 1 0 l in the male and 0 5 l in the female patients The maximum flow rate measures approximately 5 5 l/sec in the male and 3 3 l/sec in the female subjects. These differences between male and female subjects, which are so prominent in the air flow value, cannot be demonstrated for the subglottic pressure The first peak pressure is about 50 cm H_2O in both sexes The intrapleural pressure, recorded by esophageal balloon technique, was reported by Ross, Gramiak & Rahn (1955) and Whittenberger & Mead (1952) as about 100 mm Hg The difference between this intrapleural pressure and the subglottic pressure recorded in our investigations is probably the results of variations in the force of the coughs and in the high resistance of the tracheobroncheal tree

Two major patterns occur in the subglottic pressure during the positive pressure phase One type is characterized by a recoil of the pressure following the rapid fall after the first peak The other type shows only one peak pressure followed by a rapid but gradual decrease To date, we have not determined the cause of this difference However, the data obtained from breathy and forceful coughs suggest that the formation of the second peak may be related to the magnitude of the first pressure

A cough is an extremely transient phenomenon All of the physical parameters, the time, the air flow, the pressure, and the sound demonstrate constant changes The relationship between these parameters contributes to our understanding of the basic physiological mechanism Our investigations prove that there is a connection between the volume of inspired and expired air, the flow rate peak, and the first pressure peak The magnitude of the four major parameters is closely related, and so is the maximum power Thus it seems reasonable to assume that the successive dynamic stages during the positive flow phase and the positive pressure phase have been predetermined to some extent by the volume of the inspired air Any increase in the inspired air volume results in a higher flow rate peak, a higher pressure peak, and a larger expired air volume, with the production of greater power

With reference to this concept Bucher (1958) and Muller (1954) mention "The cat experiments led to the idea of a possible causal relationship between the degree of initial inspiration and the strength of the expiratory

thrust The connecting link would be the Hering Breuer reflex, i e, the fact that as lung expansion increases the activity of the inspiratory center is more and more inhibited Inhibition of inspiratory activity, however, in no way implies activation of expiration But it is not absurd to assume that thereby favourable conditions arise for the origin of cough" Bucher continues We should therefore like to propose that the inspiration immediately preceding the expiratory thrust is an integral part of the act of coughing It is an important connecting link between the stimulus and the resulting response The deeper the inspiration the stronger the expiratory thrust under otherwise equal condition" This assumption has not yet been fully proved but it receives strong support from our human experiments

A cough can be produced without a larynx, for a laryngectomized patient can expel tracheo bronchial secretions by coughing However, immediately after the operation, these patients experience great difficulty in expelling secretions According to Negus (1949) an explosive cough is no longer possible when the larynx is paralyzed or excluded from participation by the presence of a tracheostomy, the effect then resembles that of animals with no exit valve such as cows, and is consequently known as bovine Floersheim (1959) and Bucher conclude (1958) cough is also possible without the glottis Therefore closing and opening of the glottis should be considered as only a facultive auxiliary mechanism to coughing" This erroneous conclusion was reached without any attempt to determine the effectiveness of a cough, when the larynx is excluded By contrast, our present investigations prove the important contributions of the human larynx to the production of an effective cough

ZUSAMMENFASSUNG

Von einem einzelnen normalen Husten gesunder Personen wurden gleichzeitige Aufzeichnungen von Luftstromgeschwindigkeit Luftmasse subglottischem Druck und akustischem Signal angefertigt Aufeinanderfolgende Veranderungen im Widerstand an der Larynxhohe und in der Starke am subglottischen Niveau wurden in Beziehung zu diesen gemessenen Parametern verfolgt Eine Reihenfolge von Phasen wurde entsprechend spezifischen dynamischen Vorgangen klassifiziert Durchschnitts und Standardabweichungswerte der kritischen Messungen und deren Korrelationsmatrize wurden mit Hilfe von elektronischen Computern erhalten

Die Ergebnisse zeigen dass die traditionelle Beschreibung der Einatmung Kompression und Ausatmung nur eine oberflachliche Vorstellung eines ausserst komplizierten fluchtigen Phanomens gibt Ausfuhrliche Beobachtungen der physikalischen Parameter enthullen wichtige physiologische Formen Laryngologische Kontrolle der Starke und des Widerstandes ist von grosster Wichtigkeit fur die Produktion eines wirksamen Hustens Die sekundare zusatzliche Vergrosserung des Widerstandes verhindert eine Ruckkehr der ausgestossenen Substanz

Die Ergebnisse dieser Untersuchung liefern normale aerodynamische Masstabe fur vergleichende Studien von verschiedenen menschlichen Husten

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MASKING PROPERTIES OF BÁRÁNY'S NOISE BOX

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Physical measurements and audiometry were carried out to investigate the masking properties of the Bárány's Noise Box in clinical use for the conversation test. The results demonstrate that the noise box produces cross-masking of such a value as to prevent the test ear from responding to intensities lower than about 40 dB re normal speech perception threshold. As the noise of the box is very loud, 120–135 dB, the application ought to be restricted to patients not demonstrating recruitment or feebleness. Significant auditory fatigue was not registered within reasonable exposure time.

The Bárány's Noise Box is intended to mask the non-test ear during the conversation test. The noise box consists of a noise source, moved by a spring, both enclosed in a metal box. The noise is conducted through an opening in the box to a perforated olive to fit the meatal cavity. To a listener it is evident that the noise from the box must be most disagreeable when placed in the ear of the patient. The noise must furthermore be supposed to bring about cross-masking.

An inquiry made to the German factory about technical data of the noise box was negative, no data being available. We were, however, of the opinion that the physical properties of the noise box ought to be further clarified in order to decide to what extent the noise box would be suitable for clinical use.

The following questions therefore had to be explained: (1) The spectrum and the level of the noise, particularly whether these data are appropriate to the purpose, viz. masking during conversation test; (2) The masking effect in the masked ear; and (3) the masking effect in the contralateral ear (cross-masking).

It would also be of interest to clarify, if possible, cross-masking would be transferred by air, transcranially or centrally, and whether the noise in the masked ear is so loud as to cause fatigue within reasonable exposure time.

Partly physical measurements, partly audiometry were carried out. A preliminary investigation proved that the different noise boxes produced very different noises. Two copies were examined in detail. They were marked Noise Box I and Noise Box II respectively. The level and the

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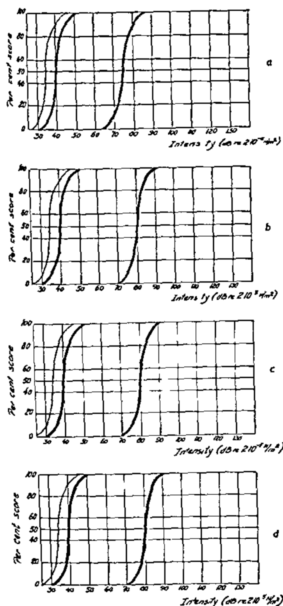


FIG 2 Monaural speech perception curve without and with the noise box in the contralateral ear (*a*) Digits Noise Box I (*b*) Digits Noise Box II (*c*) PB words Noise Box I (*d*) PB words Noise Box II

As may be noticed the normal monaural speech perception curves for digits and PB words are confluent This fact is attained by intensity equalization of the recorded Norwegian word lists On account of the above mentioned correction the intensity scales must be considered as relative and not absolute

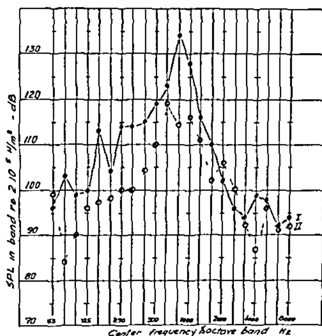


FIG 1 Spectra of the noise from Noise Box I (● ——— ●) and Noise Box II (O - - - O) measured in a 2 cm^3 coupler

spectrum were measured in a standard 2 cm^3 coupler The spectra are shown in Fig 1 The sound pressure levels were measured to be 135 dB and 121 dB respectively for the Noise Box I and the Noise Box II The SPL's obtained in these measurements are supposed to give an approximately correct idea of the features in the meatus The high noise level and the concentration of sound energy in a narrow frequency range explain why most patients report the noise to be discomfortable

In order to clarify the masking effect in the masked ear, three subjects with unilateral total deafness and normal hearing in the opposite ear were elected With the noise box placed in the hearing ear it was registered zero per cent score of the presented digits and PB words, even at the maximum intensity output level of the speech audiometer, 100 dB The speech perception threshold thus increased by at least 65 dB, which corresponds to the masking effect in the ipsilateral ear

The masking effect in the contralateral ear (cross-masking) was measured in the following way Ten normal hearing subjects were submitted to monaural speech audiometry (digits and PB words presented from a loud-speaker) Unmasked monaural conditions were obtained by covering the non-test ear with an ear defender, and masked conditions by replacing the ear defender with a noise box The masking of the non-test ear results in a marked shift of the speech perception curve Fig 2 shows the discrimination score, without and with masking in the opposite ear As the interquartile ranges are 0–5 dB, the material shows a very small spread

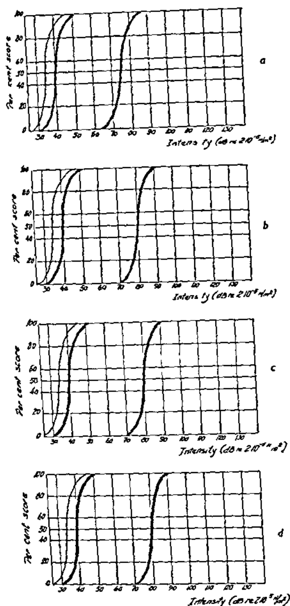


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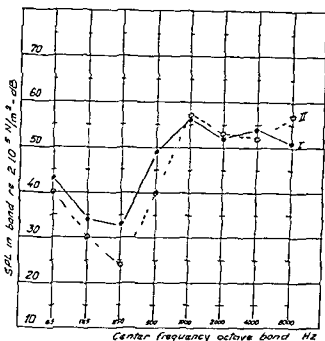


FIG 3 The noise from Noise Box I (● ——— ●) and Noise Box II (O - - - - O) measured by means of a microphone outside the contralateral ear

Fig 2 shows a contralateral shift of the speech threshold of approximately 40 dB in the normal hearing subjects The tests were repeated on three unilateral total deaf patients with the noise boxes placed in the deaf ear, showing the same result The lack of significant difference between cross-masking effect in normal hearing and in unilateral deaf subjects indicates the interaural leakage from the noise boxes to be transferred mainly transcranially, or by air, the central masking effect being negligible in this material

Fig 3 renders the spectra from direct measurements of sound transmission by air by means of a microphone placed outside the contralateral ear The levels were 60 dB and 61 dB for Noise Box I and Noise Box II respectively The sound transmission by air in these direct measurements seems to predominate in the high frequency range and to be of less value in the low frequency range

Considering the results from our physical and audiometrical measurements as a whole, the transcranial mode of transmission in our experiments seems to be the most important factor in cross-masking, but in the high frequency range the transmission by air may also contribute to cross-masking

The exposure time for noise boxes during the conversation test is supposed to be approximately 30 seconds Within this exposure time fatigue is not demonstrated in our tests, as may also be expected considering the psycho-physical facts concerning fatigue

The intensity level of the noise box is declining as the driving spring

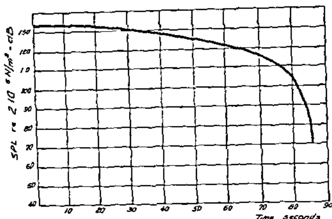


FIG 4 The intensity of Noise Box I as function of time

relaxes but not essentially during an initial period of 30 seconds after the wind up Our measurements were performed within this period The intensity as function of time is shown in Fig 4

CONCLUSION

The experiments with the noise boxes referred to demonstrate that the high intensity level together with the limited interaural insulation properties will restrict the utilization of the noise boxes during conversation tests the cross-masking effect being of such a value as to prevent the test ear from responding to intensities lower than 40 dB re normal speech perception threshold corresponding to conversation voice at a distance of about 1 metre This fact we have also demonstrated in normal hearing listeners submitted to conversation test with the noise box placed in the contralateral ear

The frequency characteristics show that the noise boxes produce a disadvantageous peak in the spectrum An elimination of this peak would to a great extent reduce the discomfort to the listener without correspondingly reducing the masking effect for speech A moderate diminishing of the overall noise level would reduce the cross masking effect and yet in most cases give a sufficient ipsilateral masking in clinical use The application of the noise boxes referred to ought to be restricted to patients not demonstrating loudness recruitment phenomenon or feebleness

ZUSAMMENFASSUNG

Um die vertäubenden Eigenschaften des Bárán振schen Lärmapparats besonders in bezug auf die klinische Verwendbarkeit des Apparates, während der Sprachgehörsprüfung zu untersuchen, haben wir physische Messungen und audiometrische Registrierungen mit der Bárány Trommel durchgeführt Die Ergeb

nisse der Untersuchungen zeigen, dass der Schalldruckpegel des Geräusches etwa 120 bis 135 dB erreicht. Das Geräusch des Bárány-Apparats vertäubt bei Normalhörigen die Sprachverständlichkeit im Maskierungsohr um wenigstens 65 dB und im Prüfungsohr um etwa 40 dB (Überhören). Wegen des hohen Schalldruckpegels des Geräusches ist es nicht ratsam, den Lärmapparat in Schallempfindungsstörungen mit Recruitment anzuwenden. Signifikante Hörermüdung wurde innerhalb der aktuellen Beeinflussungszeit nicht nachgewiesen.

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EFFECT OF ORIENTATION TO THE GRAVITATIONAL VERTICAL ON NYSTAGMUS FOLLOWING ROTATION ABOUT A HORIZONTAL AXIS

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Following clockwise rotation at 60°/sec about a horizontal cephalo caudal axis the rate of decay of nystagmic eye movements, produced by an impulsive deceleration, was significantly greater than when the axis of rotation was vertical The direction of the gravitational acceleration when normal to the axis of rotation had no consistent effect on the time constant of decay, though the angular velocity of nystagmus was greater in the 0° and 90° positions than at 180° and 270° and accounted for the larger 'nystagmus output' in the former positions Hypothetical mechanisms by which a linear acceleration may modify post rotational responses are discussed

INTRODUCTION

The nystagmus and sensation of turning produced by a rapid deceleration from rotation at constant velocity are widely used (van Egmond, Groen & Jongkees, 1948 1949) in the study of the behaviour of semicircular canal receptors In these, as in most other experiments in which canal function has been examined, the axis of rotation was vertical so that the direction of the gravitational acceleration was constant both during rotation and the ensuing post-rotational phase

Whereas several authors (Benson & Whiteside, 1961, Bergstedt, 1961, Lansberg, Guedry & Graybiel, 1964) have shown that the rate of decay and the duration of nystagmus were influenced by the direction and magnitude of the linear acceleration these experiments were carried out on centrifuges where the subjects were exposed to linear accelerations *in* excess of 1 g However more recently, Guedry (1964) and Correia & Guedry (1964) demonstrated that when subjects were rotated about a horizontal cephalo-caudal (Z) axis, and so exposed to a continual change in the direction of the gravitational acceleration the intensity of post-rotational nystagmus was reduced in comparison with that evoked by the same angular stimulus when the axis of rotation was vertical Similarly Benson & Bodin (1965) showed that when the subject was stopped in the supine position the

time constant of decay of nystagmus following rotation about a horizontal axis was approximately half of that obtained when the axis of rotation was vertical. During rotation about the horizontal axis at constant speed there was a sustained nystagmus (Guedry, 1964, Benson & Bodin, 1965) the velocity of which was modulated according to the orientation of the head to the gravitational acceleration. Characteristically during rotation to the right (clockwise), the velocity was greatest when the subject was in the left-side-down position (270°) and least when in the right-side-down position (90°). As the nystagmus induced by the rotating acceleration vector was not constant it may be inferred that the pattern of post-rotational nystagmus would differ according to the orientation of the head and synonymously the position in which the stretcher was stopped. The observations of Correia & Guedry (1964) suggested that this may be so, but their results were not conclusive. Furthermore, as their measures of post-rotational nystagmus were confined to 'nystagmus output', that is the total slow phase displacement during the 60 sec following deceleration of the subject, the *relative contribution of velocity and time constant of decay of post-rotational nystagmus* could not be assessed. Accordingly we have carried out a further series of experiments in which the time course of the post-rotational nystagmus was compared in four orthogonal orientations of the head to the gravitational vertical and with that evoked by the more conventional stimuli about a vertical axis.

METHODS

Apparatus

This has been described fully in an earlier report (Benson & Bodin, 1965). Subjects were strapped to a rigid stretcher, which could be rotated at a controlled velocity about a horizontal axis. Horizontal (*lateral*) eye movements were recorded with eyes closed by a conventional electro-oculographic technique using a DC amplifier and photographic galvanometer recorder, *on which stretcher position and velocity were also displayed*.

Subjects

The experiments were carried out on 14 members of the laboratory staff (5 female, 9 male) without clinical evidence of aural disease or abnormal vestibular function. Nine of the subjects had prior experience of the apparatus and experimental procedure. The remaining 5 subjects were examined in the rotating chair (axis of rotation vertical) before they participated in the main experiment in order to exclude any individual who produced poor quality *post-rotational nystagmus or who had significant* spontaneous horizontal nystagmus or asymmetrical responses to impulsive stimuli.

Conduct of experiment

Following application of the electrodes the subject was secured in the stretcher Calibration eye movements were recorded in the prone and supine positions With the eyes closed the stretcher was accelerated at approximately 300°/sec² to 60°/sec (±1°/sec) As earlier experiments (Benson & Bodin, 1965) had shown that the nystagmus induced by such an initial acceleration decayed to yield the characteristic sustained per-rotational nystagmus in some 15 to 20 sec the constant speed of rotation was maintained for 5 rev (30 sec) before the recorder was switched on and the stretcher stopped, some 6 sec later, in one of the four orthogonal positions These positions achieved with an accuracy of ±5°, were supine (0°), right side down (90°), prone (180°) and left-side-down (270°) From each subject post-rotational responses were recorded in each of the four positions, the order in which these were presented was varied according to a randomised design The subject was instructed to press a switch when the post rotational sensation of turning disappeared, the duration of these after-sensations being subsequently determined from the galvanometer record

Following the recording of the nystagmus induced by the four stopping stimuli further recordings were made with the subject stationary, in each of the four positions in order to assess the magnitude and direction of any spontaneous position dependent nystagmus The rate of angular movement between positions did not exceed 10°/sec and the lateral eye movements were recorded for at least 30 sec in each position

RESULTS

Post rotational sensation

As reported by Guedry (1964) and Benson & Bodin (1965), the illusory sensations of turning following rotation about a horizontal axis were very short indeed the majority of subjects did not have any sensation other than the jolt which accompanied the rapid (300°/sec²) deceleration of the stretcher This was in contrast to the normal after-sensations, with a duration of some 15 to 20 sec, which they experienced when rotated about the vertical axis and given a similar angular stimulus Three of the subjects however were able to make consistent reports about the after-sensations, the mean durations of which were 6 8 sec, 4 4 sec, 3 5 sec and 5 1 sec in the 0° 90°, 180° and 270° positions respectively Unfortunately the number of observations was insufficient to allow any conclusion to be drawn about the differences between the responses in the various stopping positions

The nature of the after-sensations differed from those experienced following rotation about a vertical axis The subjects reported that they were quite aware that the strecher had *stopped and of its* position relative to the gravitational vertical, but this veridical percept was accompanied by a sensation, which declined rapidly following the cessation of rotation, of

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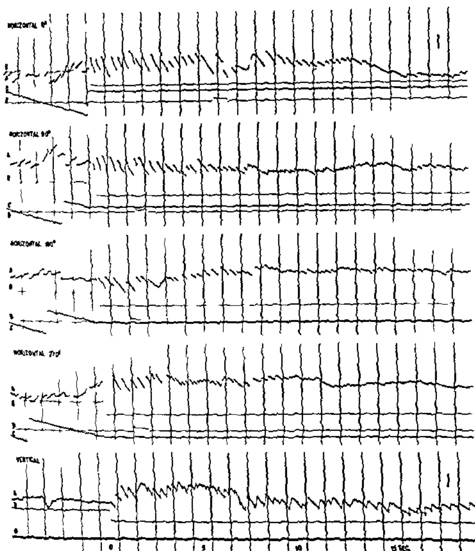


Fig 1 Records of post rotational nystagmus obtained from one subject in four horizontal positions and when the axis of rotation was vertical The traces are *A* eye movement *B* angular velocity of rotation C stretcher position *D* subject s response Vertical bar represents 10° horizontal eye movement Time markers are at 1 sec intervals

manner are shown in Fig 2 These demonstrate the appreciable reduction in the rate of decay when the axis of rotation was horizontal and the relatively small differences between the four orientations in this axis

Analysis of individual ω_n and H/Δ values showed that the contribution of the axis of rotation to the variance of the *H*/Δ values was highly significant ($p=0\,001$) However there was no consistent effect according to the position in which the stretcher was stopped The mean *H*/Δ value was least in the 90° position and greatest at 270° but because of differences

turning to the left but without significant angular movement or displacement. No consistent differences according to strecher position were apparent from the subjective assessments obtained at the end of the experiments None of the subjects experienced nausea in this experiment, in contrast to previous experiments with the rotating stretcher, probably because *in the* present procedure rotation was continued only for a relatively short period

Post-rotational nystagmus

Typical records of the nystagmic eye movements during rotation and for the 20 sec following cessation of rotation are shown in Fig 1 along with the post rotational nystagmus evoked by a similar angular stimulus when the axis of rotation was vertical Typically, on stopping the stretcher, the per-rotational nystagmus which beat with a slow phase to the left was immediately replaced by nystagmus in the opposite direction which subsequently decayed in an approximately exponential manner. The amplitude and frequency of the nystagmus was on inspection not appreciably different from that obtained when the axis of rotation was vertical, the notable difference being the more rapid decay and the shorter duration following horizontal as opposed to vertical axis rotation. In 11 subjects a well defined post-rotational nystagmus was present irrespective of the position in which the stretcher was stopped, but in the other 3 subjects the post-rotational response in one of the positions was represented by only a few nystagmic eye movements which were inadequate for quantitative analysis On two occasions these occurred in the 270° and in one *the 180° position The failure to obtain an adequate post-rotational response* was unlikely to have been associated with a low level of "arousal" (Collins & Guedry, 1962) for in 2 subjects the stimulus was the first of the series, while in the other, where it was placed third, repetition of the stimulus while the subject performed mental arithmetic failed to evoke a better *nystagmic response*

Detailed analysis of the post-rotational nystagmus was made from plots of log angular velocity of the slow phase of nystagmus against the time after stopping the stretcher The nystagmus slow phase velocity was determined by measurement of the slope of each nystagmic eye movement and converted to °/sec from the time and eye displacement calibrations As the decay of post-rotational nystagmus appeared to show an exponential time course a straight line was drawn by eye through the points and from this the time constant of decay (II/Δ) *was calculated and the angular* velocity at $t=0$ (ω_0) determined These values are assembled in Table 1 In order to obtain a representative graphical representation of the behaviour of all subjects the slow phase angular velocity during each 1 sec period for the 20 sec following deceleration was determined, and from these values *the mean* calculated for the 11 subjects who produced nystagmus in all stopping positions The mean decay curves obtained in this

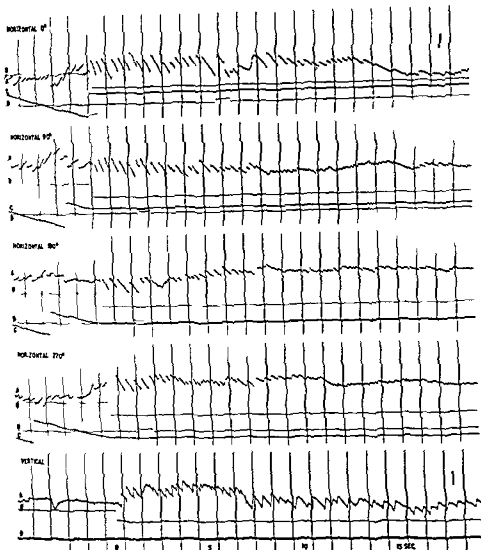


Fig 1 Records of post rotational nystagmus obtained from *one* subject *in* four horizontal positions and when the axis of rotation was vertical The *traces are A eye movement B angular velocity of rotation C stretcher position D subject's response* Vertical bar represents 10° horizontal eye movement Time markers are at 1 sec intervals

manner are shown in Fig 2 These demonstrate the appreciable reduction in the rate of decay when the axis of rotation was horizontal and the relatively small differences between the four orientations *in this axis*

Analysis of individual ω_c and H/Δ values showed that the contribution of the axis of rotation to the variance of the H/Δ values was highly significant ($p = 0.001$) However there was no consistent effect according *to the position in* which the stretcher was stopped The mean H/Δ value was least in the 90° position and greatest at 270°, but because of differences

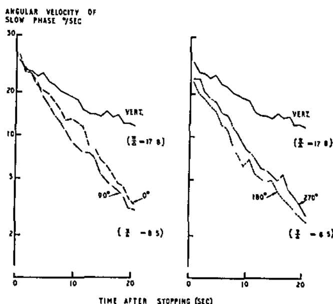


Fig 2 Pattern of decay of nystagmus in four horizontal positions and when the axis of rotation was vertical Mean of 11 subjects, each of whom received an impulsive deceleration from 60°/sec Angular velocity of slow phase nystagmus is plotted on a logarithmic ordinate scale Π/Δ values indicate time constant of decay, in seconds of lines in figure

in behaviour between subjects position was without a significant effect in the analysis of variance

The angular velocity of nystagmus at $t=0$ differed significantly ($p=0.01$) with position, being greater at 0° and 90° than in the 180° and 270° positions ($p=0.05$) The mean value of ω_{t_0} when the axis of rotation was vertical was 36.8°/sec and was similar to that observed in the 0° and 90° stopping positions from which it did not differ significantly

Horizontal nystagmus in static positions

Nystagmus was recorded with the subject stationary in the four orthogonal positions of the stretcher in the manner described earlier In all but four of the subjects nystagmus was present in one or more positions, but in general this was of low velocity (1 to 2°/sec) and was unlikely to modify the pattern of post-rotational nystagmus to an appreciable extent The direction of the nystagmus varied with position in only 2 subjects, who as it happened were excluded from the main analysis because of inadequate post-rotational responses in one of the stopping positions In the remaining 8 subjects nystagmus beat in one direction only, in three of these it was present in all positions and in one or more positions in the others

DISCUSSION

These experiments have shown unequivocally that following rotation about the horizontal axis the *rate of decay of post-rotational nystagmus*

TABLE 1 *Mean values from 11 subjects of time constant of decay (Π/Δ) and angular velocity at t = 0 (ω_t) of nystagmus and computed nystagmus output following rotation about a vertical and a horizontal axis*

	Horizontal axis					Vertical axis
	0	90	180°	270	Mean	
ω_t (°/sec)	34.6	37.6	25.8	27.9	31.4	36.8
Π/Δ (sec)	9.2	7.7	8.9	9.9	8.9	16.6
Nystagmus output (°)	298	279	214	245	259	598

was less than when a similar angular stimulus was given in the vertical axis The orientation of the head and body to the gravitational vector is thus of importance in determining the time course of decay of the nystagmic response and implies that the behaviour of the ampullary receptors or the central vestibular afferent pathways is modified by the direction of the acceleration vector Whereas several workers have demonstrated (Guedry 1964 Correia & Guedry 1964 Benson & Bodin 1965) that there was a considerable reduction in the post rotational response when the gravitational acceleration lay in the transverse plane differences related to the direction of the vector in that plane were much less clearly defined In our experiments which were confined to rotation in a clockwise direction the only consistent and significant finding was that the angular velocity of the nystagmus was less in the 180° and 270° positions than in the 0° and 90° positions The time constants of decay did not differ significantly from one another From this it may be concluded that the direction of the linear acceleration vector provided it was approximately co planar with the horizontal (lateral) canal was relatively unimportant in regulating cupular restoration

If as Timm (1953) has suggested the cupula is of greater density than the endolymph then the post rotational response following clockwise rotation should be prolonged in the right side down position (90°) and reduced when left side down (270°) there being intermediate rates of decay in the 0° and the 180° positions The analysis of variance indicated that there was no significant effect attributable to position so that comparison of individual pairs is not justifiable statistically However it is of interest that 10 out of the 12 subjects produced larger Π/Δ values at 270° than in the 90° position a difference which contradicts the theory and which implies that the cupula is less dense than endolymph This finding is also opposite to that of Correia & Guedry (1964) who showed a smaller nystagmus output at 270° than at 90° But these workers used a measure of post rotational nystagmus which is influenced by both the velocity and the rate of decay of nystagmus and represents the integral of nystagmus angular velocity from $t = 0$ to $t = 60$ sec We have computed a comparable

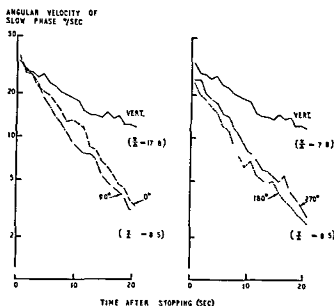


FIG 2 Pattern of decay of nystagmus in four horizontal positions, and when the axis of rotation was vertical Mean of 11 subjects each of whom received an impulsive deceleration from 60°/sec Angular velocity of slow phase nystagmus is plotted on a logarithmic ordinate scale Π/Δ values indicate time constant of decay, in seconds of lines in figure

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Nystagmus was recorded with the subject stationary in the four orthogonal positions of the stretcher in the manner described earlier In all but four of the subjects nystagmus was present in one or more positions, but in general this was of low velocity (1 to 2°/sec) and was unlikely to modify the pattern of post-rotational nystagmus to an appreciable extent The direction of the nystagmus varied with position in only 2 subjects, who as it happened were excluded from the main analysis because of inadequate post-rotational responses in one of the stopping positions In the remaining 8 subjects nystagmus beat in one direction only, in three of these it was present in all positions and in one or more positions in the others

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per-rotational nystagmus, not understood. Two theories have been proposed (Guedry, 1964, Benson & Bodin, 1965). One is that otolithic and other somaesthetic signals partially inhibit those from ampullary receptors, for in the post rotational period they carry information that the body is not turning and conflict with the inappropriate signals from the canal receptors. The other theory assumes that the direction of the acceleration vector alters the dynamic behaviour of the canal-cupula-endolymph system, in such a manner that the viscous damping of the cupula is minimal when the acceleration vector is co-planar with the canal and maximal when normal to the plane of the canal. Neither theory is without objection. The sensory interaction theory demands that the contribution of the inhibitory signal increases in intensity in an exponential manner from the moment horizontal rotation is stopped, for if the inhibitory signal reduced the vestibular afferent signal by a constant proportion, ω_{o} should have been lower in all horizontal axis positions and the time constant of decay would be the same as in the vertical axis. However the assumption of linearity within the central nervous system pathways is questionable and this argument does not negate the theory. The control of ampullary receptors by their efferent innervation is at present imperfectly understood though there is evidence (Schmidt 1963, Sala, 1965) that the activity of other vestibular receptors, and perhaps also the discharge of other somaesthetic receptors, can modulate in a predominantly inhibitary way the afferent vestibular signal. Thus the possibility arises that the interaction of efferent neural and mechanical stimulus on the ampullary receptors behaves in the non linear manner which is required by this theory.

Alteration of canal dynamics by the acceleration vector is in some ways a simpler hypothesis though this makes considerable assumptions about the anatomical configuration of the membranous canal within the bony canal according to its orientation to the gravitational vertical, assumptions which have not been substantiated by experimental observation. Until further experiments have been performed it is not possible to explain without equivocation or speculation how linear acceleration modifies the nystagmus and sensations of turning engendered by adequate stimulation of canal receptors.

ACKNOWLEDGMENTS

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ZUSAMMENFASSUNG

Nach Rechtsdrehung von 60° sec um eine horizontale cephalo-caudale Achse war die Abnahmerate nystagmischer Augenbewegungen hervorgerufen durch plötzliches Abbremsen wesentlich grosser als nach Drehung um eine vertikale

figure, given by the product of Π/Δ and ω_{t_0}, which approximates to the integral of Π/Δ from $t=0$ to $t=\infty$. The mean values obtained from 11 subjects is given in Table 2 Analysis of the individual values revealed that position made a significant contribution to the variance ($p=0.01$), with the 0 and 90° values being significantly ($p=0.01$) greater than those at 180° and 270° As it has already been demonstrated that ω_{t_0} was greater in the 0 and 90° positions than at 180° and 270°, and that the time constants did not differ significantly, it must be concluded that the differences in nystagmus velocity were more important than the rate of decay in the determination of 'nystagmus output' in the four stretcher positions Although nystagmus output in this experiment, as in that of Correia & Guedry (1964) was greater in the 90° than in the 270° position, this difference was not apparently a manifestation of a change in the dynamic behaviour of the cupula-canal-endolymph system during the post-rotational phase

During rotation about the horizontal axis nystagmus velocity was modulated in an approximately sinusoidal manner with a minimum at about 90° and maximum at 240° (Benson & Bodin, 1965) The amplitude and form of the cyclical modulations was not identical in all subjects but in general the mean nystagmus velocity during rotation at 60°/sec was about 10°/sec during the first half of the cycle and 20°/sec during the second half Now if this per-rotational nystagmus was produced by cupular deviation then it was to be expected that the post-rotational nystagmus, produced by deflection of the cupular in the opposite direction, would be reduced, when compared with the vertical axis response, by an amount equal to the velocity of the per-rotational nystagmus at the position in which the stretcher was stopped While the peak nystagmus velocity (ω_{t_0}) was less in the 180° and 270° positions than at 0° and 90° by about the anticipated 10°/sec, the ω_{t_0} values in the latter positions were almost identical with the vertical axis figures One inference from this is that cupular deflection makes only a partial contribution to the sustained per-rotational nystagmus, and is responsible only for the augmentation of nystagmus velocity during rotation in the 180° to 270° quadrant However as the mechanism by which a rotating linear acceleration vector produces nystagmus by stimulation of ampullary receptors is only conjectural (Benson & Bodin, 1965) there remains the possibility that on cessation of rotation, equilibrium of the linear acceleration mechanism is rapidly restored so that the cupula is deflected only by a force dependent on the angular deceleration which is unopposed by any associated with the linear acceleration vector

While the effect of the orientation in the horizontal axis is relatively small the decay of post-rotational nystagmus, when the axis of rotation was vertical, was consistently longer than that observed following rotation about a horizontal axis The mechanism by which the linear acceleration vector mediates this effect is, like the mechanism underlying the sustained

EFFECTS OF UNILATERAL WARM AND COLD WATER IRRIGATION IN THE OUTER EAR OF RABBITS ON ISOLATED NERVE CELLS FROM THE LATERAL VESTIBULAR NUCLEUS AND CEREBELLUM

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Two groups of rabbits were subjected to repeated cold (20°C) and warm (48°C) water irrigation, respectively, in the left outer ear for 30 minutes daily for seven days During the irrigation the animals were lightly anesthetized 24 hours after the last irrigation the animals were sacrificed Bilateral samples of isolated Deiters' giant nerve cells from the lateral vestibular nuclei were analyzed on total amount of RNA and succinoxidase activity Bilateral samples of Purkinje cells from lobulus III from the hemisphere were analyzed on total amount of RNA

After warm water irrigation there is an increase on the irrigated side of the succinoxidase activity in the Deiters' cells while the RNA content of these cells does not show any significant changes However, the amount of RNA of the Purkinje cells is increased on the irrigated side as compared to that of the cells from the contralateral side The side difference for Purkinje cells occurs even after one single irrigation After cold water irrigation the Deiters cells from the contralateral side show an increase in succinoxidase activity Still there is no change in the RNA content of these cells, but the Purkinje cells show higher RNA values for the contralateral side when compared to the irrigated side

The results seem to demonstrate that warm and cold water irrigation of one ear also influences the activity level in biochemical terms of the vestibular nuclei of the contralateral side They also demonstrate that the cerebellum at an early point takes part in the vestibular mechanism

INTRODUCTION

Hydén & Pigon (1960) demonstrated an increase in cytochrome *oxidase* and succinoxidase activity, RNA content and proteins in isolated Deiters' giant cells of the lateral vestibular nucleus *following repeated to*-and fro rotational stimulation of the rabbit The glial cells *immediately surrounding* the nerve cells were lowered with respect to these parameters during the same conditions

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Achse Die Richtung der Gravitationsbeschleunigung im Winkel von 90° zur horizontalen Drehachse hatte keine bemerkenswerte Auswirkung auf die Zeit konstante der Abnahme des Nystagmus obgleich die Winkelgeschwindigkeit in den Positionen von 0° und 90° grosser war als in den Positionen von 180° und 270°, weshalb sie fur die grossere Gesamtamplitude des Nystagmus in den erst genannten Stellungen verantwortlich zu machen ist Es werden hypothetische Mechanismen besprochen bei denen eine lineare Beschleunigung post rotationale Reaktionen verandern kann

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In a recent study the long term effect of unilateral vestibular neurotomy on the succinoxidase activity of Deiters giant nerve cells was analysed

(Hallen & Hamberger, 1964). About two weeks after the nerve section the enzyme activity on the affected side was increased 100 per cent, while the control side was unchanged Repeated to-and-fro rotational stimulation of the animals during the week prior to the cell analyses caused a complete inhibition of the observed increase in enzyme activity

These findings raised a number of questions regarding partly the cerebellar-reticular formation system, which is supposed to be engaged in maintaining the balance between the vestibular nuclei of both sides, partly the effect of unilateral vestibular stimulation with special regard to the effect on the contralateral vestibular nuclei

Warm and cold water irrigation, respectively, of one ear, was chosen as the simplest way of obtaining a physiological unilateral stimulation The RNA content and succinoxidase activity of the Deiters' giant nerve cells and RNA content of the Purkinje cells of cerebellum were studied

In subsequent papers the distribution of the stimulatory effect within the cerebellum and a comparative study of RNA and respiratory enzymes will be reported

MATERIAL AND METHODS

Albino rabbits, weighing between 1400–1700 g, were used

Calorization Procedure

Two groups of rabbits were subjected to repeated water irrigation in the left outer ear for 30 minutes once daily for seven days, one group at 20°C and the other at 48°C The animals were sacrificed about 24 hours after the last irrigation

All animals were anesthetized intravenously by nembutal (0 4 ml/kg= 24 mg/kg body weight) and fixed on a table The head was held in such a position that the lateral semicircular canals were vertically oriented The ears were pulled upwards and fixed to a bar A fine rubber tube (about one mm diameter) was introduced with the tip close to the drum membrane, its position being checked under the operation microscope

The water supply, warm and cold, respectively was taken from two temperature regulated containers placed about one meter above the level of the animal The temperature was checked in the tube immediately before its entrance in the ear as well as in the water flowing out of the ear

In some animals a spontaneous nystagmus was evoked after the anesthesia About 20–30 seconds after the beginning of the irrigation nystagmus adequate to the caloric stimulation was achieved The frequency of the eye movements were followed throughout each irrigation

RNA Determinations

Pieces of cerebellum and medulla oblongata were removed immediately after death and fixed in Carnoy's solution (i e absolute ethanol, chloro-

form concentrated acetic acid 6/3/1 by volyme) for 90 minutes The pieces of tissue were embedded in paraffin and cut at 50 μ From the sections single cells were isolated by micromanipulation and extracted with ribo nuclease in an oil chamber according to Edstrom (1953) The extracts collected were evaporated to dryness on a quartz glass and redissolved in glycerol containing buffer, forming lens shaped drops The drops were photographed in ultraviolet light at a wavelength of 257 mμ together with a reference system The amounts of RNA in the ultraviolet absorbing spots were determined by a microphotometric procedure

Determination of Enzyme Activity

The microdissection technique of Hyden & Pigon (1960) was used and the oxygen consumption was measured with Zeuthen's micro diver tech nique (Zeuthen 1953)

Slices from the medulla oblongata were cut through the lateral vestibular nucleus The Deiters giant nerve cells were dissected out freehand together with the surrounding glial cells which were subsequently separated from the neurons by gentle manipulation with the dissecting instrument in a drop of incubation medium Each nerve cell was introduced into separate micro divers along with a small volume of succinoxidase incubation me dium In this way nerve cells from the right and left sides were analyzed during each diver experiment Oxygen consumption was determined mano metrically for 2–3 hours and was expressed as 10^{-4} μl O_2 per sample per hour

RESULTS

Deiters Cells

RNA

The results are presented in Table 1 A total number of 156 cells are analyzed from four animals exposed to repeated warm water irrigation in the left ear In no case a significant difference between the RNA amount of the right and left side was found The results do not exclude a small side difference concealed by the errors of the sampling and method

Succinoxidase

The nerve cells of the unstimulated side have in both cases an enzyme activity somewhat higher than that which is observed with control animals The warm water reproduces the increase on the side on which the ear is irrigated while the cold water induces a contralateral increase

The nerve cells of the unstimulated side have in both cases an enzyme activity somewhat higher than that which is observed with control animals This finding emphasized earlier reports that the untreated side of the vestibular system cannot function as a control (Hallén & Hamberger 1964)

TABLE 1. *Determinations of RNA in nerve cells of the lateral vestibular nucleus of the rabbit.*

Determinations carried out on samples of 1–4 cells
Effect of warm (48°C) and cold (20°C) water irrigation 30 minutes per day for seven days in the left outer ear

Rabbit	Mean value in μμg		±S.E.M. per cell		Percentage higher on the left side
	Left	*n*	Right	*n*	
(a) 48°C 7×30 min					
1	1091±42	4	1045±77	6	4 4
2	1094±72	6	1175±54	6	−7 4
3	1348 (1469) (1228)	2	1082±33	3	24 6
4	1294±54	5	1185±41	6	9 2
Mean	1207±67		1122±35		7 6
(b) 20°C 7×30 min					Percentage higher on the right side
1	1356± 72	12	1396±72	15	2 9
2	1398± 39	4	1274±42	6	−8 9
3	976±124	3	1078 (992) (1165)	2	10 5
4	851± 56	4	1339±73	3	57 3
Mean	1145±136		1272±60		11 1

n = Number of cells

TABLE 2. *Succinoxidase activity in Deiters' giant nerve cells of the lateral vestibular nucleus of the rabbit*

Enzyme activity expressed as 10^{-4} μl O_2 per hour Mean values±S.E.M.
Effect of warm (48°C) and cold (20°C) water irrigation 30 minutes per day for seven days in the left outer ear

Left side	*n*	Right side	*n*	P
(a) 48°C 7×30 min				
4 6±0 3	5	2 9±0 3	6	<0 02
(b) 20°C 7×30 min				
3 2±0 6	9	5 9±0 8	7	<0 02

n = Number of animals

TABLE 3 *Succinoxidase activity in Deiters' giant nerve cells of the lateral vestibular nucleus of the rabbit.*

Enzyme activity expressed as 10^{-4} µl per hour Mean values ± S.E.M
Effect of one single exposition to cold (20°C) water irrigation (30 min)

Left side	*n*	Right side	*n*
2 9 ± 0 4	7	3 1 ± 0 4	9

n = Number of animals

The results after a single cold water irrigation (Table 3) give no evidence of a side difference in the nerve cells

Purkinje Cells

RNA

Preliminary investigations were carried out to ascertain that no difference between the left and right side of the cerebellum normally exists No such difference could be observed, with regard to RNA content of Purkinje cells in unstimulated rabbits

For RNA determinations, the lobulus III from hemisphere was selected

TABLE 4 *Determinations of RNA in Purkinje cells taken from hemisphere, lobulus III*

Determinations carried out on samples of two cells
Effect of warm (48°C) and cold (20°C) water irrigation 30 minutes per day for seven days in the left outer ear

Rabbit	Mean value in µµg ± S.E.M per cell				Percentage higher on the left side
	Left	*n*	Right	*n*	
(a) 48 C 7 × 30 min					
1	250 + 18 0	6	233 ± 8 8	6	7.3
2	287 ± 9 0	6	254 ± 20 1	6	13 0
3	244 ± 17 2	6	197 ± 7 0	6	23 9
4	231 ± 5 4	6	164 ± 5 0	6	40 9
5	289 ± 13 3	6	258 ± 7 0	6	12 0
(b) 20°C 7 30 min					
1	230 ± 3.6	6	238 ± 7 0	6	20 5
2	296 ± 6 1	6	328 ± 9 2	6	11 2
3	219 ± 6.1	6	251 ± 12.3	6	11 6
4	256 ± 6 3	6	261 ± 11 4	6	2 0

P = Value for the whole material $P < 0.001$
n = Number of samples

TABLE 5 *Determinations of RNA in Purkinje cells taken from hemisphere lobulus III*

Determinations carried out on samples of two cells
The animals calorized once with cold water (20°C–30 min)

	Mean value in $\mu\mu g$		± S E M		
Rabbit	Left	*n*	Right	*n*	Percentage higher on the right side
1	177±10 3	6	237±16 2	6	33 9
2	151±21 5	5	212± 9 4	6	40 4

P = Value for the whole material $P < 0\ 01$
n = Number of samples

Determinations were carried out on samples of two cells It was found that in animals calorized with warm water in the left ear, the Purkinje cells taken from this side held a significant higher RNA content than those from the right side (Table 4)

In animals calorized with cold water the results show a significantly lower RNA content in the Purkinje cells taken from the calorized side when compared with the cells from the contralateral side Thus, the findings here are quite opposite to the findings when the animals were calorized with warm water (Table 4) A similar side difference as after repeated irrigations is observed after one single cold water irrigation (Table 5)

DISCUSSION

The results obtained show that following repeated unilateral warm water irrigation of one ear in rabbits, an increased succinoxidase activity in the Deiters' giant nerve cells appears on the experimental side, while the RNA content of the cells is not significantly altered Under the same conditions there is an increase in the total RNA of the Purkinje cells of cerebellum taken from hemisphere lobulus III on the same side as the warm water irrigation compared to the contralateral side

After repeated cold water irrigation the succinoxidase activity of Deiters' cells is increased to a similar extent as with warm water irrigation, but the effect is now on the contralateral side Similarly the RNA content of the Purkinje cells on the contralateral side is also increased It should be emphasized that cold and warm water stimulation actually lead to an absolute increase in succinoxidase activity After a single exposure to cold water irrigation, no changes are observed in the Deiters' cells while the RNA content of the Purkinje cells shows the same side difference as after repeated irrigations

A fundamental point in a study of this type is the evaluation of RNA content and succinoxidase activity as indicators of cell function Both parameters

have been studied in several works from this laboratory after different types of physiological stimulation of the experimental animal Hydén & Pigon (1960), after repeated to and fro rotational stimulation of rabbits, showed increases concerning both succinoxidase activity and RNA content in the Deiters' cells In other studies, respiratory enzymes as well as respiration glucose consumption and RNA content have shown changes as a result of increased function (Chentsov, Borovyagin & Brodskii, 1961, Geiger, 1962, McIlwain 1955) A comparison of the succinoxidase activity and the RNA content changes indicates a strong parallel between the two parameters as judged from the work of Hyden & Pigon (1960) and the present experiments The changes however, as calculated in percentage difference from the control are small for RNA when compared with the enzyme, i e in the Deiters' cells The internal parallel is thus somewhat broken as a moderate increase in succinoxidase activity is not necessarily accompanied by a significant increase in RNA, as is the case in the Deiters' cells in the present experiments However, recent experiments indicate that there is a definite differentiation between RNA content and succinoxidase activity as indicators of cell function (Blomstrand, Hallen Hamberger & Jarlstedt to be published)

The findings of Walberg, Bowsher & Brodal (1958) indicate that no primary vestibular fibres reach the Deiters giant cells The primary fibres which reach the other nerve cells of the lateral vestibular nucleus seem to originate only from the utriculus and not from the semicircular canals It is then most probable that the effect on the Deiters' giant cells is mediated by secondary vestibular fibres from one or more of the other vestibular nuclei cerebellum reticular formation or possibly still other sources

The distinct difference in RNA content between the Purkinje cells from the right and left side of the cerebellum appears after one single cold water irrigation At this time no significant effect was observed in the enzyme activity of the Deiters' cells This demonstrates that at least the cerebellum at an early point is involved in regulating the disturbed balance within the vestibular system As the RNA difference in the cerebellar cells would reflect an increased activity the physiological effect of cerebellar stimulation on the activity of the vestibular nuclei needs some consideration It is known from the works of Dow (1939) that single shocks applied to vestibular structures produce ipsilaterally evoked potentials in the flocculonodular lobe the uvula IX lingula I RNA changes have been found in these areas as well as in lobulus centralis III (Jarlstedt, to be published) Responses were found in both hemispheral and vermian portions of these areas The works of de Vito Brusa & Arduini (1956) and Pompeiano & Cotti (1959) deal with recording the activity in the nerve cells of nucleus Deiters during electrical stimulation of different parts of cerebellum Inhibition was produced in some cells and facilitation in others The fastigial nucleus complicates the interpretation of the data demonstrated among others by Moruzzi & Pompeiano (1957) This is due both to its anatomical

TABLE 5. *Determinations of RNA in Purkinje cells taken from hemisphere, lobulus III.*

Determinations carried out on samples of two cells
The animals calorized once with cold water (20°C–30 min)

Rabbit	Mean value in $\mu\mu g$ ± S.E.M. Left	n	Right	n	Percentage higher on the right side
1	177 ± 10.3	6	237 ± 16.2	6	33.9
2	151 ± 21.5	5	212 ± 9.4	6	40.4

P = Value for the whole material $P < 0.01$
n = Number of samples

Determinations were carried out on samples of two cells. It was found that in animals calorized with warm water in the left ear, the Purkinje cells taken from this side held a significant higher RNA content than those from the right side (Table 4).

In animals calorized with cold water the results show a significantly lower RNA content in the Purkinje cells taken from the calorized side when compared with the cells from the contralateral side. Thus, the findings here are quite *opposite to the findings* when the animals were calorized with warm water (Table 4). A similar side difference as after repeated irrigations is observed after one single cold water irrigation (Table 5).

DISCUSSION

The results obtained show that following repeated unilateral warm water irrigation of one ear in rabbits, an increased succinoxidase activity in the Deiters' giant nerve cells appears on the experimental side, while the RNA content of the cells is not significantly altered. Under the same conditions there is an increase in the total RNA of the Purkinje cells of cerebellum taken from hemisphere lobulus III on the same side as the warm water irrigation compared to the contralateral side.

After repeated cold water irrigation the succinoxidase activity of Deiters' cells is increased to a similar extent as with warm water irrigation, but the effect is now on the contralateral side. Similarly the RNA content of the Purkinje cells on the contralateral side is also increased. It should be emphasized that cold and warm water stimulation actually lead to an absolute increase in succinoxidase activity. After a single exposure to cold water irrigation, *no changes are observed in the Deiters' cells while the* RNA content of the Purkinje cells shows the same side difference as after repeated irrigations.

A fundamental *point* in a study of this type is the evaluation of RNA content and succinoxidase activity as indicators of cell function. Both parameters

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position close to the cortico-vestibular pathways and to its important functional coordination of the cerebello-vestibular connections. The main result, when Purkinje cells are concerned, is that participation of cerebellum in the vestibular system is chemically established, mainly suggesting a homolateral inhibitory effect on the giant cells of lateral vestibular nucleus.

As mentioned in the introductory part, one of the aims of this study was to obtain some information about the contralateral effect of unilateral labyrinthine stimulation. To and fro rotational stimulation of an animal having the vestibular nerve cut on one side resulted in an inhibition of the increase in succinoxidase activity otherwise observed on the side of vestibular neurotomy. Electrical stimulation of the vestibular nerve on one side produces a blocking of the spontaneous activity of the nerve cells in the vestibular nuclei on the contralateral side (de Vito, Brusa & Arduini 1956). We have, due to the complexity of this system, not obtained straightly analogous results. Referring to the current view, a warm water irrigation would produce an opposite effect. The results after cold water irrigation strengthen in a way the electrophysiological data and explain the findings in our earlier work: the cold water irrigation stimulates the contralateral side. The underlying reactions may not be the same, but we find it strongly suggestive that we have demonstrated the contralateral effect in biochemical terms, although we have applied inhibition instead of stimulation.

ZUSAMMENFASSUNG

Zwei Gruppen von Kaninchen wurden sieben Tage täglich 30 Minuten mit kaltem Wasser (+20 C) beziehungsweise warmem Wasser (+48 C) kalorisch stimuliert. Die Spülung wurde unter leichter Anästhesie durchgeführt. 24 Stunden nach der letzten Spülung wurden die Kaninchen getötet. Isolierte Deiters Riesenzellen der beiderseitigen lateralen vestibulären Kerne wurden mit Hinsicht auf die totale Menge RNS und Succinoxidaseaktivität analysiert. Purkinjezellen in der Hemisphäre des III. Lobulus von beiden Seiten wurden im Hinblick auf die totale Menge RNS hin analysiert.

Nach Warmwasserspülung findet man eine Zunahme der Succinoxydaseaktivität in den Deiterszellen auf der gespülten Seite, während die RNS-Menge keine merkbare Veränderung zeigt. Die RNS-Menge in den Purkinjezellen zeigt jedoch eine Zunahme, verglichen mit Zellen der kontralateralen Seite. Diese Seitenunterschiede bei den Purkinjezellen zeigen sich auch nach einmaliger Spülung. Nach Kaltwasserspülung zeigen die Deiterszellen auf der kontralateralen Seite eine Zunahme der Succinoxidaseaktivität, während die RNS-Menge unverändert blieb. Die Purkinjezellen auf der kontralateralen Seite zeigen, verglichen mit Zellen der homolateralen Seite, erhöhte RNS-Mengen.

Das Resultat zeigt, dass Warm- und Kaltwasserspülung eines Ohres das Aktivitätsniveau, gemessen mit biochemischen Parametern, sowohl in dem lateralen Vestibulariskern als auch im Cerebellum beeinflusst. Solche Veränderungen können auch auf der kontralateralen Seite abgelesen werden, desgleichen dass das Cerebellum schneller Veränderungen zeigt als die Vestibulariskerne.

of phase between the sound stimulus at the external canal and the potentials recorded directly from the cochlea A phase shift as indicated by a change in the shape of the Lissajous figure was taken to indicate a change in the latent period He reported that 0 5–1 mg of physostigmine given intra arterially to a guinea-pig weighing 500 g prolonged the latency by 0 1–0 2 millisecs, 1–2 minutes after injection As a result of these experiments and others with physostigmine, hexastigmine and fluostigmine, he concluded that cholinesterase inhibitors influence the time it takes for sound waves in the cochlea to be transduced into electrical potentials as they are manifested in the Wever and Bray effect

Davis (1957) doubted the participation of acetylcholine in the generation of cochlear potentials and described Gisselsson's observations as "puzzling In a later study Deatherage, Eldredge & Davis (1959) measured the latency of the action potentials recorded with intra-cochlear electrodes and found it varied with the intensity and frequency of the acoustic stimulus, but did not discuss the question of electrical *vs* chemical transmission In his review "Some Principles of Sensory Receptor Action" Davis (1961) reconsidered the possibility of chemical transmission at the synapse between the hair cells and the auditory nerve endings

The presence of acetylcholinesterase in the cochlea was first demonstrated by Churchill Schuknecht & Doran (1956) They found strong concentrations of this substance in the nerve endings surrounding the inner hair cells and postulated that it was associated with the endings of the olivo-cochlear bundle this they confirmed three years later (Schuknecht, Churchill & Doran, 1959) Vosteen (1961) in his review concludes that "acetylcholine is the active substance of the efferent nerve fibres and is not involved in the afferent process of sound transformation"

Vinnikov & Titova (1964), having satisfied themselves that acetylcholinesterase is present in the hairs of both the inner and outer hair cells of the organ of Corti, take the point of view that acetylcholine is involved in both afferent and efferent pathways They believe that the movement of the hairs through the acetylcholine loaded endolymph brings about a depolarisation of the hair cell membrane and the consequent excitation of the whole cell body which results in the appearance of the cochlear microphonic

From our review of the literature on this subject it became apparent that the work of Gisselsson occupies a key position in this controversy Those who favour acetylcholine as the chemical mediator regard his evidence as convincing proof The uncommitted writers view his observations as puzzling and frankly contradictory to all other observations and interpretations

We were thus prompted to re-examine the effect of physostigmine on the latency of the cochlear potentials For this purpose a new and essentially simple technique for directly measuring the latency of the cochlear microphonic and the action potential was devised and used for the first time in the experiments described in this paper

THE EFFECT OF PHYSOSTIGMINE ON THE LATENCY OF THE COCHLEAR POTENTIALS

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One of the main pieces of evidence favouring the participation of acetylcholine in the generation of nerve impulses in the cochlea is the reported prolongation of the latency of the cochlear potentials following injections of physostigmine Direct measurements of the latencies of the cochlear microphonic (CM) and the nerve action potential (AP) in guinea pigs using a new on line technique are described in this paper Our investigation confirmed that the latency of the CM remains stable while that of the AP varies inversely with temperature Intravenous injections of physostigmine did not change the latency of either CM or AP as anticipated Some very small irregular changes were noted accompanying violent systemic reactions to the drug It is concluded that systemic injections of physostigmine do not prolong the latency of either CM or AP and we surmise that previous reports of this effect were due to undetected temperature changes

The recent publication of *The Organ of Corti* by Vinnikov & Titova (1964) stimulated us to review the evidence for the participation of acetylcholine in the generation of the cochlear microphonics and the action potentials in the auditory nerve fibres

Derbyshire & Davis (1935) seem to have been the first to suggest that a chemical mediator might be involved in the generation of nerve impulses in the fibres of the auditory nerve Martini (1941) and Dacha & Martini (1942) showed that acetylcholine appeared in the perilymph of pigeons exposed to sound and concluded that exposure to sound leads to the liberation of acetylcholine in the cochlea Gisselsson (1950) was not able to confirm these findings in a variety of experimental animals including man

According to Vinnikov & Titova (1964) the most convincing proof of the presence of acetylcholine in the endolymph was the finding by Gisselsson (1950) that injections of physostigmine and other cholinesterase inhibitors led to a lengthening of the latent period of the cochlear potentials The method used by Gisselsson did not measure the latent period directly but used Lissajous patterns displayed on an oscilloscope to indicate changes

This work is supposed in part by the Medical Research Council of Canada

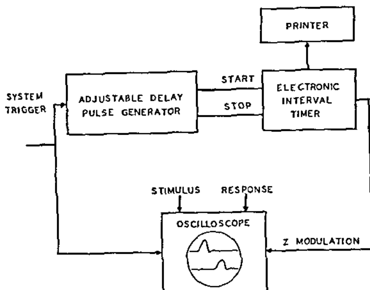


FIG 2 Time delay measuring equipment

3 *Measurement of latency*

A new technique for the measurement of response latency was devised especially for these experiments The experimenter observes the stimulus and response wave forms on the face of the oscilloscope However on the trace there are two markers in the form of bright spots which can be moved anywhere along the horizontal axis of the face of the cathode ray tube One spot is lined up with the onset of the stimulus the other with the particular peak of the response whose latency is to be measured The time between the two spots is thus the required latency As the spots are marker pulses generated by an electronic timer at the start and stop of a time interval measurement and fed into the Z input of the observation oscilloscope the time interval between the spots i e the latency is displayed on the readout panel of the counter and printed out simultaneously (Fig 2) Details of the technique and equipment will be published elsewhere

This technique has several advantages over the methods which are normally used to measure latency of which the most significant is the elimination of photography It thus becomes unnecessary to visualize both stimulus and response on the same trace and any amount of sweep expansion may be used to allow the precise placement of the leading edge of the bright spot at the exact point to be measured With this method very small variations in latency are easily noted especially if the trace is viewed through a binocular magnifier As the pulses are repetitive the position of the response can be determined by observation and the measure

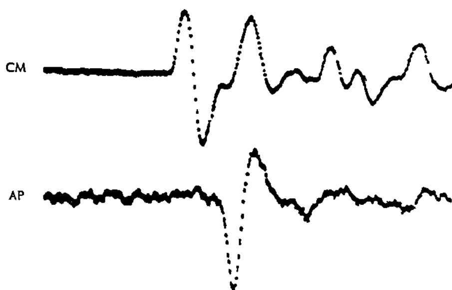


FIG 1 Cochlear microphonic (CM) and nerve action potential (AP) responses to a click stimulus recorded from Turn I of the guinea-pig cochlea

METHODS

1 *Recording of potentials*

The technique used to record the cochlear microphonic and nerve action potential responses to sound stimulation is similar to that described by Tasaki, Davis & Legouix (1952) Differential electrodes were inserted into the basal turn of the cochlea and the potential changes amplified and displayed on two oscilloscopes The main advantage of this type of recording is that the cochlear microphonic and the nerve action potential can be displayed separately and their latencies measured independently

2 *Acoustic stimulus*

The major difficulty in the precise measurement of latency is to determine the exact time of occurrence of the events being measured In order to facilitate the measurements, we used a stimulus with a very distinct onset The source of the signal was a Hewlett–Packard Signal Generator Type 205 AG adjusted for a frequency of 2000 cps as measured by a CMC Type 226 B Counter-Timer The signal was then fed to an electronic gate of our own manufacture which was set to produce pulses consisting of a single half-cycle of the 2000 cps tone at a rate of ten per second These pulses were fed to a University PA–HF loudspeaker pressure unit through a McIntosh 75 watt amplifier and control attenuators The clicks thus produced were conducted through a plastic tube to a speculum sewn in the external meatus of the guinea-pig This signal was chosen because it gave cochlear microphonic (CM) and nerve action potential (AP) responses of a very distinct and simple wave-form (Fig 1).

1 *Preliminary series*

These experiments duplicated those of Gisselsson except for the method of recording *the CM and AP and measuring the latencies* Temperature measurements were not made initially Intraperitoneal injections of 0.3 to 1.0 mg of physostigmine salicylate were given to guinea pigs weighing between 300–550 g It was anticipated that this dosage would prolong the latency by 0.1 to 0.2 millisecs In fact the results of these first eight experiments were variable Prolongation of the latency of the AP was sometimes seen to occur during the course of the experiment On other occasions it did not change or became shorter The latency of the CM response never showed any change

It became apparent during these experiments that the temperature of the animal was of significance in determining the latency of the AP but not that of the CM A search of the literature revealed a paper by Kahana Rosenblith & Galambos (1950) which reported similar findings in the hamster From this we concluded that the variability of response referred to earlier was due to the changing temperature of the animal At the start of a recording session a hot water bottle was routinely placed beneath the animal Thus, during the recording session the animal's temperature slowly rose remained steady and then fell Depending on the time of injection of the physostigmine we observed a shortening no change or a prolongation of the latent period It most often happened that physostigmine was injected after a half hour period of recording By this time the temperature *of the animal was beginning to fall and a prolongation of the AP* latency was recorded which we wrongly ascribed to the physostigmine Our error was proved beyond doubt when we observed a similar response to an injection of distilled water

As a result in the subsequent experiments the temperature was very carefully monitored throughout using the technique described

2 *The effect of temperature*

A number of experiments were done to determine the effect of temperature change on the latency of the CM and AP Measurements of latency *vs temperature were made in 15 animals using the techniques described* Temperature changes were induced by placing hot or cold bottles beneath the animal Temperature, latency and time were recorded simultaneously The results showed that (*a*) the CM latency does not change with temperature, regardless of whether the latency is measured to the start first positive or first negative peaks of the CM response (*b*) the AP latency changes linearly with temperature over the *range* 29.5°C–36.5°C Over this range, latency shortens as temperature rises Outside these limits the latency tends to change less as the temperature increases *or decreases* (Fig. 3)

ment printed out when the observer is satisfied that the spot is in the correct location

Variations in latency of 10 microseconds are easily observed and the repeatability of measurement is ±2 microseconds In the preliminary experiments the latencies were measured at two levels of stimulation, 20 db and 30 db above the AP threshold as observed on the oscilloscope With electrodes in Turn I of the cochlea, times from the onset of the stimulus to the onset of the cochlear microphonic (S-CM) and from the onset of the stimulus to the peak of the action potential (S–AP) were measured From these measurements the time CM–AP was calculated

In the later experiments one stimulus level 30 db above AP threshold was used and measurements were made to the first positive peak of the CM response For all levels of stimulation and measurements of latency the results were qualitatively the same

4 *Measurement of temperature*

In the preliminary experiments the animal's temperature was measured with a Yellow Springs Instruments 402 Probe placed in the rectum However, it became obvious that there was a considerable lag between changes in the rectal temperature and their effect on the cochlea when the animal was warmed or cooled with a hot water bottle placed beneath the body Subsequently, the probe was inserted into the pharynx at the level of the cochlea As a result, measured changes in temperature and their observed effect on the cochlea became virtually simultaneous, indicating a close correspondence between the pharyngeal and cochlear temperatures (The work of Gulick & Cutt (1962) supports this assumption) With our equipment changes in temperature of 0 1°C could be measured accurately

EXPERIMENTS AND RESULTS

For this study we used guinea-pigs, weighing between 300 and 550 g anaesthetized with Dial (CIBA) The results of experiments on 22 animals are reported The first difficulty encountered was obtaining a stable preparation, i e one in which the latencies of the CM and AP remained constant over a significant period of time with the sound pressure of the stimulus kept constant In resolving this problem we became aware that many factors affected the latencies as measured by this method Fluid collecting in the bulla, changes in the amplitude of the AP response for whatever reason changes in the temperature of the animal, and changes in the depth of anaesthesia all apparently affected the latency of the responses In some instances, the effect of these factors was determined more precisely and will be discussed later In other instances, measures were taken to eliminate these factors as a source of variation Throughout all these experiments we were struck by the stability of the latency of the CM response under all conditions except when the death of the animal was imminent

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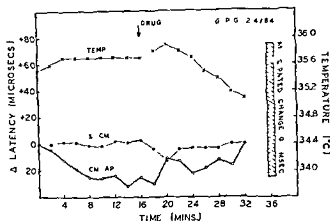


FIG 4 Changes in latency of cochlear microphonic and nerve action potential following injection of maximal sub-lethal dose of physostigmine Note variation of CM–AP time with temperature Vertical hatched bar shows anticipated change in CM–AP time following injection of the drug

DISCUSSION

The primary purpose of this investigation was to test the effect of physostigmine on the latency of the cochlear microphonics (CM) and the nerve action potentials (AP) as recorded by differential electrodes placed in the guinea pig cochlea So far as we know, the only study of this subject was the one by Gisselsson to which we have already referred, who reported that physostigmine produced a prolongation of the latency of the cochlear potentials

Unfortunately, our experiments do not confirm these findings, and we are forced to conclude that physostigmine injected intra-venously has no direct effect on the latency of either CM or AP

Our experiments differ from those reported by Gisselsson in several respects Firstly, we were able to record the CM and AP independently of each other Secondly we measured the latencies of the separate potentials directly with a high degree of accuracy, and thirdly, by using small thermistor probes we could reliably measure the temperature very close to the cochlea

Judging from his report, Gisselsson (1950) made a most careful study of the effects of the intensity of sound stimulation, the duration of the experiment and changes in blood pressure on the latency of the cochlear potentials In his experiments on the effects of physostigmine he allowed for or eliminated any variation in latency due to these factors At about the same time, Kahana Rosenblith & Galambos (1950) were just completing their work on the effects of temperature on the latency of the cochlear potentials in the hamster, so Gisselsson did not have the advantage of knowing that changes in temperature have a very significant effect on the la-

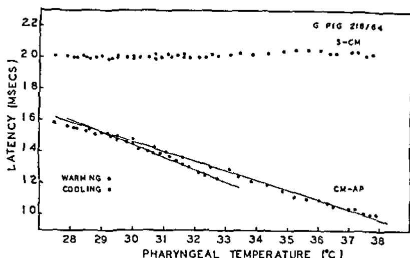


Fig 3 Relation between temperature and latency of CM and AP responses S–CM = time from onset of electrical signal to loudspeaker to first positive peak of CM and includes time taken for sound to travel from loudspeaker to tympanic membrane and generation of cochlear microphonics CM–AP = time from first positive peak of CM to first negative peak of AP and includes time taken for transmission of excitation from hair cells to auditory nerve endings and conduction of nerve impulses to internal auditory meatus

3 *The effect of physostigmine*

Because our method for measuring latencies is very sensitive even small variations in temperature cause easily detectable changes in AP latency It was decided not to attempt precise control of the animal's body temperature, but to monitor it at one-minute intervals so that any changes could be detected and the effect on the AP latency determined

Physostigmine was injected through an intravenous cannula It was given in varying dosage up to and including the lethal dose The effects of physostigmine are well known, in small doses it causes increased mobility of the gastro-intestinal tract, bladder and bowel evacuation, in large doses it also affects skeletal muscle causing generalised fibrillary twitchings In our experiments the effect of the dose was monitored by observing the occurrence of these phenomena throughout the course of the experiment Although the intensity of the effects varied with the dose given, they were always observed There is no doubt that in all our experiments the drug entered the circulation and was distributed throughout the body

Altogether 20 injections of physostigmine were given, varying in dosage from 0 05 mg to 1 0 mg i v In no instance did we observe any change in latency, either of AP or CM, which could be specifically attributed to the action of physostigmine on the cochlea In some instances transient changes in the latency of the CM and AP were seen These changes were small, inconsistent, of short duration, and were always associated with a violent systemic reaction to the drug (Fig 4)

vascularis Yamamoto & Nakai (1964) showed recently that dextrin-iron particles 100 Å in diameter appeared in the capillaries of the stria vascularis and spiral ligament within 10 minutes of intravenous injection of 5 per cent dextrin iron solution. As physostigmine salicylate, the preparation used in these experiments has a molecular weight of 431.6 it would seem reasonable to suppose that it would behave in much the same way as fluorescein and would be distributed in the endolymph and perilymph very promptly following intravenous injection. However, even if we assume that physostigmine freely circulates throughout the endolymph and perilymph, we still cannot be certain that it reaches the hair cells and the synaptic gap between them and the endings of the afferent and efferent neurons in a sufficient concentration to affect the generation of either the CM or AP. The uncertainties with regard to the ultimate distribution of the injected physostigmine in these experiments preclude any final judgment on the question of the role of acetylcholine in the generation of the cochlear potentials.

ACKNOWLEDGMENTS

Mr Robert C. Rivard is thanked for his invaluable assistance.

ZUSAMMENFASSUNG

Einer der Hauptbeweise, der die Teilnahme von Acetylcholin in der Erzeugung von Nervenimpulsen in der Cochlea begünstigt, ist die erwähnte *Verlangerung* der Latenz des Cochlearpotentials die der Injektion von Physostigmin *folgt*. Direkte Bestimmungen der Latenzen des cochlearen mikrophonischen Potentials (CM) und des Nervenaktionspotentials (AP) in Meerschweinchen, die eine *neue* Auf-der-Linie Technik benutzen sind in diesem Artikel *beschrieben*. *Unsere* Untersuchungen bestätigen dass die *Latenz des CM stabil bleibt*, während die des AP im umgekehrten Verhältnis zur Temperatur variiert. Intravenöse Injektionen von *Physostigmin änderten* — wider Erwarten — weder die Latenz von CM noch die *von* AP. *Einige sehr* kleine, unregelmässige Veränderungen, die heftige systematische Reaktionen *zum* Physostigmin begleiteten, waren festzustellen. Man kam zu dem Schluss dass *systemische* Injektionen von Physostigmin weder die Latenz von CM noch die von AP verlängern, und wir vermuten, dass vorhergegangene Berichte dieses Effektes *auf* unbemerkte Temperaturschwankungen zurückzuführen waren.

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tency of the AP, a finding since confirmed by Fernandez, Singh & Perlman (1958)

It is well known that guinea-pigs anaesthetised with solutions containing urethane lose their temperature regulation and become poikilothermic Normal body temperature for this animal is 38–39°C As room temperature is usually 21–23°C an anaesthetised guinea-pig cools rather rapidly unless specific measures are taken to prevent this happening Under these circumstances in our laboratory, the body temperature drops 7 to 8°C in about two hours, if not controlled According to our measurements (Fig 3) this would produce a change in AP latency of 0 5 millisecond or more, which is considerably greater than the 0 1 to 0 2 millisecond changes noted by Gisselsson which could be accounted for by a change of less than 2°C

From our experience we have found that if the temperature is not measured, changes in latency may be seen which occur as a result of undetected variations in the temperature of the animal In explaining our different findings, it is perhaps significant that Gisselsson did not report measuring or controlling the temperature of his experimental animals Thus, it is possible that the prolongation of latency he described may have been due to temperature changes

At first sight it might seem that the partial elimination of the effect of physostigmine by preceding injections of atropine, as was reported by Gisselsson, proves conclusively that the effects noted were specific to the drug However, we have observed that atropine in large doses delays the fall in body temperature which occurs as a result of the loss of temperature regulation This would have the effect of partially eliminating the prolongation apparently caused by the physostigmine

One further point needs explanation As we have previously remarked the latency of the CM is extremely stable, in contrast to the latency of the AP which is quite labile It is well known that the cochlear potentials as recorded by Gisselsson, i e with one electrode at the apex of the cochlea and the other on the neck consist of a mixture of CM and AP (Davis Gernandt & Riesco-MacClure, 1950, Davis, Fernandez & McAuliffe, 1950) Therefore, the changes he noted in the latency of the cochlear potentials were probably due to changes in the AP component of the response and thus not indicative of any effect on the generation of the cochlear microphonic This assumption would be consistent with our own observations and others (Kahana, Rosenblith & Galambos 1950) on the stability of the CM response

As we failed to find an effect for physostigmine we must ask the question as to whether physostigmine injected intravenously reached the cochlea Jako *et al* (1959) showed that fluorescein (molecular weight 332 30) injected intravenously into the guinea-pig reached the cochlea within 6 minutes, being distributed in both endolymph and perilymph Substances with a much higher molecular weight, e g Trypan Blue (molecular weight 960 81) take longer to reach the cochlea and remain confined to the stria-

vascularis Yamamoto & Nakai (1964) showed recently that dextrin iron particles 100 A in diameter appeared in the capillaries of the stria vascularis and spiral ligament within 10 minutes of intravenous injection of 5 per cent dextrin iron solution As physostigmine salicylate the preparation used in these experiments has a molecular weight of 434 6 it would seem reasonable to suppose that it would behave in much the same way as fluorescein and would be distributed in the endolymph and perilymph very promptly following intravenous injection However, even if we assume that physostigmine freely circulates throughout the endolymph and perilymph we still cannot be certain that it reaches the hair cells and the synaptic gap between them and the endings of the afferent and efferent neurons in a sufficient concentration to affect the generation of either the CM or AP The uncertainties with regard to the ultimate distribution of the injected physostigmine in these experiments preclude any final judgment on the question of the role of acetylcholine in the generation of the cochlear potentials

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IN SEARCH OF TONIC CERVICAL REFLEXES

An Evaluation of Fukuda's Vertical Writing Test

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In view of Fukuda's report that it is possible to demonstrate tonic cervical reflexes by means of his vertical writing test, a study was made of the variations occurring in vertical writing by blindfolded and non-blindfolded individuals: these variations proved to be greater than those assumed by Fukuda. Next, an attempt was made to establish whether this method can be used to trace tonic cervical reflexes which have so far not been demonstrable in normal human behaviour. Our study did not confirm Fukuda's test results.

A. Fukuda's Blindfolded Vertical Writing Test

Since the publications of Magnus & de Kleyn (1912, 1915, 1925) clinical and experimental work has focused more on research on nystagmus than on the tonic cervical reflexes. Wodak (1927, 1953, 1957) and Guttich (1925, 1942) made a plea in favour of a study of the "deitero-spinal reflexes" which Fukuda (1959, 1961) attempted to register by his "blindfolded vertical writing test" (BVWT).

Technique

The test subject sits upright on a chair at a table, the head pointing straight ahead with no part of the body touching the table; the sole contact with the table is that of the point of the pencil used to write. The first six letters are written downwards in a vertical row, first of all with the eyes open (test I), thereafter with the eyes covered (test II). The slant of the row is determined as indicated in Fig. 1.

Experiment

We examined 200 normal subjects without ear diseases, between the ages of 17 and 25 years.

Results

1. In test I, 9 subjects were capable of writing down a vertical row, 148 subjects deviated to the right ($>0°$), whilst 43 showed a negative deviation ($<°$); average 1.9°, standard deviation 2.8°.

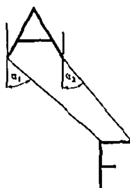


Fig. 1. Slant of the row of letters $= (\angle\alpha_1 + \angle\alpha_2)/2$

2. In test II, 2 subjects could write a vertical row, 89 deviated to the right (>0°) and 109 to the left (<0°); average −3.6°, standard deviation 8°.

3. Comparing test II with test I (i.e. with the subjective normal) we found 1 subject with an identical reaction, 116 deviated to the left and 83 to the right of their subjective normal.

4. A deviation <6° was seen in 91 subjects, between 6° and 10° in 66 subjects and between 10° and 26° in 43 subjects.

Conclusion

We cannot agree with the assumption that a slant of 6° or more indicates an instability of the labyrinthine system.

B. *The Influence of a Rotated Head Position on the Direction of Vertical Writing*

Magnus & de Kleyn (1912, 1915) demonstrated that in decerebrate subjects rotation of the head causes flexion of the "crown arm" and extension of the "chin arm". This asymmetrical tonic neck reflex, which the discoverers never saw in normal adults, can be seen in young infants (Landau 1923, Schaltenbrand 1925, Peiper & Isbert 1927, and others; see Willemse 1961).

Fukuda claimed the possibility of demonstrating the reflex by means of his BVWT. When a test subject is blindfolded and asked to write down a vertical row of letters, the slant of the series is alleged to be to the right when the head is rotated to the left, and vice versa.

Experiment I

In 200 subjects aged 17–25, without ear diseases, we attempted to evaluate the BVWT.

Taking the normal straight head position as initial value, rotation to the left represents an angle of 90°, while the subsequent rotation to the

TABLE 1

Head rotated to	Slant[a] of the vertical direction of writing to	Code
Left	Right	R L
Right	Left	
Left	Left	L R
Right	Right	
Left	Right	R R
Right	Right	
Left	Left	L L
Right	Left	

[a] Relative to the personal subjective vertical (i e the direction of writing with the head looking straight ahead)

right then represents an angle of 180° To prevent possible labyrinthine components from playing an unequal role, we took rotation of the head *either* to the left *or* to the right as a starting point

One hundred test subjects started with the head rotated to the left (L), next wrote with the head looking straight ahead (N) and then with the head rotated to the right (R) LNR series I

One hundred other test subjects started with the head rotated to the right (R), next wrote with the head looking straight ahead (N) and then with the head rotated to the left (L) RNL series II

The two N-values of series I and II are comparable Statistical analysis of the data indicated no significant difference between the N-value in series I and that in series II so that the order of sequence does not appear to influence N

There are 4 possible combined reaction patterns which were coded as indicated in Table 1

Results

With the head in the three positions described the slant of the vertical row of letters written with the eyes covered was determined per test subject The mean values and the standard deviation are indicated in Table 2

In every test subject moreover, we determined whether following rotation of the blindfolded head a deviation of the slant of the letter row occurred as compared with the subjective "vertical" row written down blindfolded with the head in the neutral position The sign test was used in analysing these data, this analysis therefore, supplies no data on the extent of the deviation (Table 3)

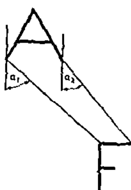


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Experiment I

In 200 subjects aged 17–25, without ear diseases, we attempted to evaluate the BVWT.

Taking the normal straight head position as initial value, rotation to the left represents an angle of 90°, while the subsequent rotation to the

Discussion

Rotation of the head to the right gives results which do not differ conspicuously from those found with the head in the neutral position This means that, in the 4 possible combined reaction patterns of this factor (Table 1), no systematic contribution to the result can be expected

In series I rotation of the head to the left proves to be associated with a marked tendency to deviate to the right (Table 2) This may well determine the high *RL* (reaction according to Fukuda), another argument in favour of this is the high *RR* (RL+RR=64) ($\chi^2=5\ 7 \rightarrow 0\ 02>p>0\ 01$)

In series II, rotation of the head to the left is associated with a deviation to the left (Table 2) It could be predicted that *LR* and *LL* would then often be seen, this was indeed the case (LR+LL=62) ($\chi^2=5\ 0 \rightarrow 0\ 05>p>0\ 02$)

These findings seem to warrant the *conclusion that, by means of the vertical writing test, it is not possible to demonstrate that a tonic cervical reflex plays a role in normal adults as assumed by Fukuda*

Consistency

If a systematic factor influences the distribution of the 4 possible combined reaction patterns, then repetition of the experiment could be expected to yield a similar result

Experiment II

Some months later 73 of the test subjects repeated the BVWT, 39 worked in the sequence L\R, 34 in the sequence R\L

Results

The mean values and standard errors of the 73 subjects in both experiments are presented in Table 4

TABLE 4

(See also Table 2)

Sequence L\R ($n=39$)	m	σ	Sequence R\L ($n=35$)	m	σ
Exp I A			*Exp I B*		
L	2 2	8 9	R	1 5	8 7
\	−0 3	8 9	\	0 9	8 1
R	−1 1	12	L	−1 4	7 1
Exp II A			*Exp II B*		
L	5 9	8 8	R	1 8	10 0
\	1 9	10 2	\	3 5	10 6
R	−0 4	10 2	L	0 2	9 5

TABLE 2.

Series I	Sequence LNR	100 test subjects
L	$m = 3.38°$	$\sigma = 8$ –
N	$m = -.56$	$\sigma = 9$ –
R	$m = -1.10$	$\sigma = 10$ –
Series II	Sequence RNL	100 test subjects
R	$m = -0.19$	$\sigma = 8$ –
N	$m = -0.16$	$\sigma = 8$ –
L	$m = -2.49$	$\sigma = 8$ –

Coding L = head to the left N = head in neutral position, R = head to the right
Calculation $m = \sum fx/n$ (average deviation in degrees relative to 0°) $\sigma = \sqrt{\sum fx^2/n}$ ($n = 100$)

TABLE 3

(For code cf Table 1)

	RL	LR	RR	LL
Series I (LNR)	34	21	30	15
Series II (RNL)	16	29	22	33

Conclusions

1 Comparison of the values in series I and II shows that only the mean values found with the head to the left (L) differ significantly from the other (NR) values [1]

In series I, $Z = 2$ –, $p = 0.05$, in series II, $Z = 3$ –, $p = 0.01$ In neither series do N and R differ

2 Only the values with the head turned to the left (cf Table 2), therefore, show an unmistakable deviation This deviation is to the right of 0° (or to the right of N) if the head is rotated to the left as the commencing attitude (series I), it is to the left of 0° (or to the left of N) if the head is rotated to the left as the terminal attitude (series II) This means that the occurrence of a deviation depends on rotation of the head to the left, while the direction of the deviation depends on the arrangement of the test

3 The frequency distribution in series I does not correspond with a probability distribution ($\chi^2 = 8.8$ $0.05 > p > 0.02$) A systematic factor probably plays a role in this respect

Relations in series II are less straightforward ($\chi^2 = 6.8$ $0.10 > p > 0.05$)

[1] $Z = m_1 - m_2 / \sqrt{\frac{\sigma_1^2}{n} + \frac{\sigma_2^2}{n}}$

Conclusion

It has thus been established that a Magnus & de Kleyn reflex *cannot be demonstrated with the vertical writing test.*

C. *Theoretical Considerations*

The fact that considerable inter-individual and intra-individual variability was seen in the results of the Fukuda test is not surprising. Magnus and de Kleyn were only able to demonstrate the mechanism of tonic cervical reflexes under pathological conditions (e.g. decerebration). This situation, in which man lives a relatively "isolated" life (Goldstein, 1934) and is greatly limited in his relationship to his environment, is characterized by more pronounced constancy and rigidity of his reaction patterns. In that case reflexes *can* become the sole mode of behaviour as a consequence of the organic limitations (cf. Merleau-Ponty, 1953). Fukuda's stepping test (1959)—a method of investigation which can be compared with Unterberger's "Tretversuch" (1938)—also fails to yield the well-defined results which its author expects. Blindfolded test subjects with extended forward arms were asked to "mark time" for a few minutes. "*Normal right handed* persons may show slight left rotation of the body, and normal left handed ones slight right deviation of the body" (pages 89–100). In two independent investigations neither Zilstorff-Pedersen & Peitersen (1963) nor Jordan (1963) could confirm these results. It seems probable that not only "a revision of the present concept of vestibular activity" (Jordan) is indicated, but the question must be raised *whether normal human behaviour can indeed be regarded as the final result of a complex of necessary reflexes.*

Comparing the tonic cervical reflexes with, say, the patellar reflex, we find that the latter can also be provoked under "normal" conditions (without decerebration) but even this reflex has a variability which is far more impressive than its apparent constancy. Bowditch & Warren had already recognized this (1890) and extensive re-investigations, among others by Paillard (1955) has irrefutably established this fact.

The demonstration of a reflex *pattern* in a free behaviour situation indicates a possible rather than a necessary form. Fukuda's photographs on posture in sports can therefore be replaced by other photographs demonstrating the opposite pattern.

ZUSAMMENFASSUNG

Anlässlich Fukudas Mitteilung dass es möglich wäre mittels seines vertikalen Schreibtestes tonische Halsreflexe nachzuweisen wurde zunächst eine Untersuchung der Variationen *beim* vertikalen Schreiben an Versuchpersonen mit und ohne verbundene Augen vorgenommen, wie *sich* herausstellte, waren diese grösser als Fukuda es annimmt. Sodann wurde *geprüft ob* mit dieser Methode

TABLE 5

(Cf. Table 1)

Sequence LNR and Series I ($n = 39$)	RL	LR	RR	LL	Sequence RNL and Series II ($n = 35$)	RL	LR	RR	LL
Exp. I	13	10	11	5	Exp. I	5	10	9	11
Exp. II	13	2	14	10	Exp. II	[illegible]	5	12	16
Identical	4	1	5	2	Identical	—	3	3	4

In every test subject the L and R values were compared with the N values (see Table 5). Again the sign test was used for this.

Conclusions

1. Of the results presented in Table 4 only L and N as well as L and R of experiment II A show a significant difference ($p = 0.03$ and $p = 0.001$ respectively). Similar to the first experiment with 100 test subjects (Table 2) a deviation to the right accompanied rotation of the head to the left. Experiment II B shows a similar trend but this is not sufficiently significant: rotation of the head to the left is accompanied by a deviation to the left ($p = 0.08$).

2. In experiment II A $RL + RR$ ($= 27$) is again significantly different from $LR + LL$ ($= 12$) – ($\chi^2 = 5.7 \to 0.05 > p > 0.02$).

In experiment II B the opposite effect is not observed, in agreement with the nonsignificant difference between R and N. The $RL + RR$ ($= 14$) in this case does not significantly differ from $LL + LR$ ($= 21$) ($\chi^2 = 1 \to p > 0.10$).

3. Of the 73 test subjects 22 produced the same result as far as direction is concerned when the test was repeated; only 4 of these showed the reaction described by Fukuda (RL).

4. Subsequently an attempt was made to determine whether the number of identical reactions in experiments I and II might differ from what might occur by chance. For this purpose the observed frequency (12 and 10 in series LNR and RNL respectively) was compared with the frequency predicted on the basis of probability.[1]

The Z values found (0.52 for LNR and 0.15 for RNL) indicate that these frequencies do not differ, so that the number of identical reactions in series I and II of experiments I and II can be explained exclusively on the basis of coincidence.

[1] $Z = (X - n \cdot p + 0.5) / \sqrt{n \cdot p \cdot q}$ in which X = number of identical values, n = number of test subjects, $q = 1 - p$. $p = \frac{13}{39} \cdot \frac{13}{39} + \frac{10}{39} \cdot \frac{2}{39} + \frac{11}{39} \cdot \frac{14}{39} + \frac{5}{39} \cdot \frac{10}{39}$ (for series LNR).

Conclusion

It has thus been established that a Magnus & de Kleyn reflex *cannot be demonstrated with the vertical writing test*

C Theoretical Considerations

The fact that considerable inter-individual and intra-individual variability was seen in the results of the Fukuda test is not surprising Magnus and de Kleyn were only able to demonstrate the mechanism of tonic cervical reflexes under pathological conditions (e g decerebration) This situation, in which man lives a relatively "isolated' life (Goldstein, 1934) and is greatly limited in his relationship to his environment, is characterized by more pronounced constancy and rigidity of his reaction patterns In that case reflexes *can* become the sole mode of behaviour as a consequence of the organic limitations (cf Merleau Ponty, 1953) Fukuda's stepping test (1959)—a method of investigation which can be compared with Unterberger's 'Tretversuch' (1938)—also fails to yield the well-defined results which its author expects Blindfolded test subjects with extended forward arms were asked to "mark time" for a few minutes 'Normal right-handed persons may show slight left rotation of the body, and normal left handed ones slight right deviation of the body' (pages 89–100) In two independent investigations neither Zillstorff-Pedersen & Peitersen (1963) nor Jordan (1963) could confirm these results It seems probable that not only "a revision of the present concept of vestibular activity" (Jordan) is indicated but the question must be raised *whether normal human behaviour can indeed be regarded as the final result of a complex of necessary reflexes*

Comparing the tonic cervical reflexes with, say, the patellar reflex, we find that the latter can also be provoked under "normal' conditions (without decerebration), but even this reflex has a variability which is far more impressive than its apparent constancy Bowditch & Warren had already recognized this (1890), and extensive re-investigations, among others by Paillard (1955) has irrefutably established this fact

The demonstration of a reflex pattern in a free behaviour situation indicates a possible rather than a necessary form Fukuda's photographs on posture in sports can therefore be replaced by other photographs demonstrating the opposite pattern

ZUSAMMENFASSUNG

Anlässlich Fukudas Mitteilung dass es möglich wäre, mittels seines vertikalen Schreibtestes tonische Halsreflexe nachzuweisen wurde zunächst eine Untersuchung der Variationen beim vertikalen Schreiben an Versuchpersonen mit und ohne verbundene Augen vorgenommen, wie sich herausstellte, waren diese grösser als Fukuda es annimmt Sodann wurde geprüft ob mit dieser Methode

die bisher im normalen menschlichen Verhalten nicht nachweislichen tonischen Halsreflexe sich ausfindig machen liessen Wir konnen auf Grund unserer Untersuchung Fukudas Versuchsergebnisse nicht bestatigen

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